

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization  
International Bureau



(43) International Publication Date  
26 April 2001 (26.04.2001)

PCT

(10) International Publication Number  
WO 01/29009 A1

(51) International Patent Classification<sup>7</sup>: C07D 239/42,  
401/12, A61K 31/505, A61P 9/14

(21) International Application Number: PCT/GB00/04043

(22) International Filing Date: 19 October 2000 (19.10.2000)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:  
9924862.7 20 October 1999 (20.10.1999) GB

(81) Designated States (*national*): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States (*regional*): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

(71) Applicant (*for all designated States except US*): CELL-TECH CHIROSCIENCE LIMITED [GB/GB]; 216 Bath Road, Slough, Berkshire SL1 4EN (GB).

**Published:**

- With international search report.
- Before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments.

(72) Inventors; and

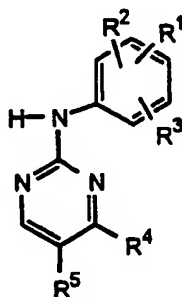
(75) Inventors/Applicants (*for US only*): DAVIS, Jeremy, Martin [GB/GB]; 372 London Road, Wokingham, Berkshire RG40 1RE (GB). MOFFAT, David, Festus, Charles [GB/GB]; 14 Lonsdale Way, Holyport, Maidenhead, Berkshire SL6 2YX (GB).

*For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.*

(74) Agents: HALLYBONE, Huw, George et al.; Carpmaels & Ransford, 43 Bloomsbury Square, London WC1A 2RA (GB).

(54) Title: 4,5-DISUBSTITUTED-2-AMINOPYRIMIDINES

WO 01/29009 A1



(1)

(57) Abstract: Pyrimidines of formula (1) are described, wherein R<sup>1</sup> is a -XR<sup>6</sup> group; R<sup>2</sup> and R<sup>3</sup> which may be the same or different is each a hydrogen or halogen atom or a group selected from an optionally substituted aliphatic, cycloaliphatic, heteroaliphatic, heterocycloaliphatic, -OH, -OR<sup>10</sup> [where R<sup>10</sup> is an optionally substituted aliphatic, cycloaliphatic, heteroaliphatic, heterocycloaliphatic, aromatic or heteroaromatic group] -SH, -NO<sub>2</sub>, -CN, -SR<sup>10</sup>, -COR<sup>10</sup>, S(O)R<sup>10</sup>, -SO<sub>2</sub>R<sup>8</sup>, -SO<sub>2</sub>N(R<sup>8</sup>)(R<sup>9</sup>), -CO<sub>2</sub>R<sup>8</sup>, -CON(R<sup>8</sup>)(R<sup>9</sup>), -CSN(R<sup>8</sup>)(R<sup>9</sup>), -NH<sub>2</sub> or substituted amino group; R<sup>4</sup> is a X<sup>1</sup>R<sup>11</sup> group where X<sup>1</sup> is a covalent bond or a -C(R<sup>12</sup>)(R<sup>13</sup>)-[where each of R<sup>12</sup> and R<sup>13</sup> is a hydrogen or halogen atom or a hydroxyl, alkyl or haloalkyl group] or -C(O)- group and R<sup>11</sup> is an optionally substituted phenyl, thienyl, thiazolyl or indolyl group; R<sup>5</sup> is a halogen atom or an alkynyl group; and the salts, solvates, hydrates and N-oxides thereof. The compounds are selective KDR kinase and/or FGFR kinase inhibitors and are of use in the prophylaxis and treatment of disease

states associated with angiogenesis.

#### **4.5-DISUBSTITUTED-2-AMINOPYRIMIDINES**

5 This invention relates to certain 4,5-disubstituted-2-aminopyrimidines, to processes for their preparation, to pharmaceutical compositions containing them, and to their use in medicine.

10 Angiogenesis, the growth of capillaries from existing blood vessels, is an essential process in normal embryonic development, tissue repair and some aspects of female reproductive function. It is also associated with the development of several pathological disorders including solid tumour growth, metastasis, psoriasis and rheumatoid arthritis, as well as diabetic retinopathy and age related macular degeneration (Folkman, Nature Medicine, (1995) 1, 27-310).

15 Several growth factors have been shown to mediate angiogenesis through alteration of vascular permeability, including vascular endothelial growth factor (VEGF; G. Breier *et al.*, Trends in Cell Biology, 1996, 6, 454-6), platelet derived growth factor (PDGF) and acidic and basic fibroblast growth factors (a & b FGF).

20 VEGF in dimeric form is a ligand that binds to two transmembrane tyrosine kinase associated receptors, expressed exclusively on proliferating endothelial cells, KDR (Flk-1 in mice) also known as VEGFR-2, and Flt-1 also known as VEGFR-1. Binding of VEGF to KDR/Flk and Flt leads to receptor dimerisation, kinase activation, autophosphorylation of the receptor and phosphorylation of intracellular substrates. An analogous series of events ensues after ligand occupancy of the more widely expressed tyrosine kinase associated FGFR receptor by aFGF or bFGF.

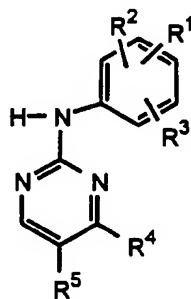
25 Thus receptor tyrosine kinase activity initiates a cellular signalling pathway leading to proliferation.

30 Antagonism of VEGF with antibody completely suppresses neovascularisation and growth of human rhabdomyosarcoma A673 spheroids in athymic mice (Borgstrom *et al.*, Cancer Res., 1996, 56 4032-4039). Suppression of bFGF gene expression by interferons  $\alpha$  and  $\beta$

inhibits capillary density in mice, leading to pancreatic eyelet tumour suppression (Folkman *et al*, Proc. Natl. Acad.Sci. 1996, 93, 2002 and Singh *et al* Proc.Natl. Acad. Sci. 1995, 92, 10457). Other receptor associated kinases such as PDGF $\beta$  and EGFr may also have some role in  
 5 mediating angiogenesis.

We have now found certain 4,5-disubstituted-2-aminopyrimidines which are potent and selective inhibitors of receptor tyrosine kinases involved in angiogenesis, especially KDR kinase and/or FGFr kinase. Selective  
 10 inhibition of these kinases can be expected to have a beneficial effect and the compounds are thus of use in the prophylaxis and treatment of disease states associated with angiogenesis, as described hereinafter.

Thus, according to one aspect of the invention, we provide a compound of  
 15 formula (1):



(1)

wherein R<sup>1</sup> is a -XR<sup>6</sup> group [where X is a covalent bond, -O-, -S-, -C(O)-, -C(S)-, -C(O)O-, -S(O)-, -S(O<sub>2</sub>)-, -CH<sub>2</sub>-, -or N(R<sup>7</sup>)- [where R<sup>7</sup> is a hydrogen atom or a straight or branched alkyl group] and R<sup>6</sup> is a hydrogen or halogen atom or an optionally substituted aliphatic, cycloaliphatic, heteroaliphatic, heterocycloaliphatic, aromatic or heteroaromatic group, or a -NO<sub>2</sub>, -CN, -SO<sub>2</sub>N(R<sup>8</sup>)(R<sup>9</sup>) [where R<sup>8</sup> and R<sup>9</sup>, which may be the same or different is a hydrogen atom or an optionally substituted aliphatic, cycloaliphatic, heteroaliphatic, heterocycloaliphatic, aromatic or heteroaromatic group], -CON(R<sup>8</sup>)(R<sup>9</sup>), -CSN(R<sup>8</sup>)(R<sup>9</sup>), -NH<sub>2</sub> or substituted amino group;  
 20  
 25

- R<sup>2</sup> and R<sup>3</sup> which may be the same or different is each a hydrogen or halogen atom or a group selected from an optionally substituted aliphatic, cycloaliphatic, heteroaliphatic, heterocycloaliphatic, -OH, -OR<sup>10</sup> [where R<sup>10</sup> is an optionally substituted aliphatic, cycloaliphatic, heteroaliphatic, heterocycloaliphatic, aromatic or heteroaromatic group] -SH, -NO<sub>2</sub>, -CN, -SR<sup>10</sup>, -COR<sup>10</sup>, S(O)R<sup>10</sup>, -SO<sub>2</sub>R<sup>8</sup>, -SO<sub>2</sub>N(R<sup>8</sup>)(R<sup>9</sup>), -CO<sub>2</sub>R<sup>8</sup>, -CON(R<sup>8</sup>)(R<sup>9</sup>), -CSN(R<sup>8</sup>)(R<sup>9</sup>), -NH<sub>2</sub> or substituted amino group;
- R<sup>4</sup> is a X<sup>1</sup>R<sup>11</sup> group where X<sup>1</sup> is a covalent bond or a -C(R<sup>12</sup>)(R<sup>13</sup>)- [where each of R<sup>12</sup> and R<sup>13</sup> is a hydrogen or halogen atom or a hydroxyl, alkyl or haloalkyl group] or -C(O)- group and R<sup>11</sup> is an optionally substituted phenyl, thienyl, thiazolyl or indolyl group;
- R<sup>5</sup> is a halogen atom or an alkynyl group;
- and the salts, solvates, hydrates and N-oxides thereof.
- 15 In the compounds of formula (1), the term "optionally substituted aliphatic group" when applied to each of the groups R<sup>2</sup>, R<sup>3</sup>, R<sup>6</sup> and R<sup>10</sup> means each of these groups may independently be for example an optionally substituted C<sub>1-10</sub> aliphatic group, for example an optionally substituted straight or branched chain C<sub>1-6</sub> alkyl, e.g. C<sub>1-3</sub> alkyl, C<sub>2-6</sub> alkenyl, e.g. C<sub>2-4</sub> alkenyl, or C<sub>2-6</sub> alkynyl, e.g. C<sub>2-4</sub> alkynyl group. Each of said groups may
- 20 be optionally interrupted by one or two heteroatoms or heteroatom-containing groups represented by X<sup>2</sup> [where X<sup>2</sup> is an -O- or -S- atom or a -C(O)-, -C(S)-, -S(O)-, -S(O)<sub>2</sub>-, -N(R<sup>14</sup>)- [where R<sup>14</sup> is a hydrogen atom or a C<sub>1-6</sub> alkyl, e.g. methyl or ethyl, group], -CON(R<sup>14</sup>)-, -OC(O)N(R<sup>14</sup>)-, -CSN(R<sup>14</sup>)-, -N(R<sup>14</sup>)CO-, -N(R<sup>14</sup>)C(O)O-, -N(R<sup>14</sup>)CS-, -SON(R<sup>14</sup>), -SO<sub>2</sub>N(R<sup>14</sup>), -N(R<sup>14</sup>)SO<sub>2</sub>-, -N(R<sup>14</sup>)CON(R<sup>14</sup>)-, -N(R<sup>14</sup>)CSN(R<sup>14</sup>)-, -N(R<sup>14</sup>)SON(R<sup>14</sup>)- or -N(R<sup>14</sup>)SO<sub>2</sub>N(R<sup>14</sup>) group] to form an optionally substituted R<sup>2</sup>, R<sup>3</sup>, R<sup>6</sup> and R<sup>10</sup> heteroaliphatic group.
- 30 Particular examples of aliphatic groups represented by R<sup>2</sup>, R<sup>3</sup>, R<sup>6</sup> and/or R<sup>10</sup> include optionally substituted -CH<sub>3</sub>, -CH<sub>2</sub>CH<sub>3</sub>, -(CH<sub>2</sub>)<sub>2</sub>CH<sub>3</sub>, -CH(CH<sub>3</sub>)<sub>2</sub>, -(CH<sub>2</sub>)<sub>3</sub>CH<sub>3</sub>, -CH(CH<sub>3</sub>)CH<sub>2</sub>CH<sub>3</sub>, -CH<sub>2</sub>CH(CH<sub>3</sub>)<sub>2</sub>, -C(CH<sub>3</sub>)<sub>3</sub>, -(CH<sub>2</sub>)<sub>4</sub>CH<sub>3</sub>, -(CH<sub>2</sub>)<sub>5</sub>CH<sub>3</sub>, -CHCH<sub>2</sub>, -CHCHCH<sub>3</sub>, -CH<sub>2</sub>CHCH<sub>2</sub>, -CHCHCH<sub>2</sub>CH<sub>3</sub>, -CH<sub>2</sub>CHCHCH<sub>3</sub>, -(CH<sub>2</sub>)<sub>2</sub>CHCH<sub>2</sub>, -CCH, -CCCH<sub>3</sub>, -CH<sub>2</sub>CCH, -CCCH<sub>2</sub>CH<sub>3</sub>, -CH<sub>2</sub>CCCH<sub>3</sub>, or -(CH<sub>2</sub>)<sub>2</sub>CCH groups. Where
- 35 appropriate each of said groups may be optionally interrupted by one or

two atoms and/or groups  $X^2$  to form an optionally substituted heteroaliphatic group. Particular examples include  $-\text{CH}_2\text{X}^2\text{CH}_3$ ,  $-\text{CH}_2\text{X}^2\text{CH}_2\text{CH}_3$ ,  $-(\text{CH}_2)_2\text{X}^2\text{CH}_3$  and  $-(\text{CH}_2)_2\text{X}^2\text{CH}_2\text{CH}_3$  groups.

- 5 The optional substituents which may be present on these aliphatic and/or heteroaliphatic groups include one, two, three or more substituents selected from halogen atoms, e.g. fluorine, chlorine, bromine or iodine atoms, or hydroxyl,  $\text{C}_{1-6}$  alkoxy, e.g. methoxy or ethoxy, thiol,  $\text{C}_{1-6}$  alkylthio e.g. methylthio or ethylthio,  $-\text{SC}(\text{NH})\text{NH}_2$ ,  $-\text{CH}_2\text{C}(\text{NH})\text{NH}_2$ , amino, substituted amino, cyclic amino or heteroaromatic groups.

Substituted amino groups include for example groups of formulae  $-\text{NR}^{15}\text{R}^{16}$  [where  $\text{R}^{15}$  is an optionally substituted  $\text{C}_{1-6}$  alkyl,  $\text{C}_{2-6}$  alkenyl or  $\text{C}_{2-6}$  alkynyl group optionally interrupted by one or two heteroatoms or heteroatom-containing groups represented by  $\text{X}^3$  (where  $\text{X}^3$  is an atom or group as described above for  $\text{X}^2$ ) and  $\text{R}^{16}$  is a hydrogen atom or is a group as just defined for  $\text{R}^{15}$ ],  $-\text{N}(\text{R}^{16})\text{COR}^{15}$ ,  $-\text{N}(\text{R}^{16})\text{CSR}^{15}$ ,  $-\text{N}(\text{R}^{16})\text{SOR}^{15}$ ,  $-\text{N}(\text{R}^{16})\text{SO}_2\text{R}^{15}$ ,  $-\text{N}(\text{R}^{16})\text{CONH}_2$ ,  $-\text{N}(\text{R}^{16})\text{CONR}^{15}\text{R}^{16}$ ,  $-\text{N}(\text{R}^{16})\text{C}(\text{O})\text{OR}^{15}$ ,  $-\text{N}(\text{R}^{16})\text{C}(\text{NH})\text{NH}_2$ ,  $-\text{N}(\text{R}^{16})\text{C}(\text{NH})\text{NR}^{15}\text{R}^{16}$ ,  $-\text{N}(\text{R}^{16})\text{CSNH}_2$ ,  $-\text{N}(\text{R}^{16})\text{CSNR}^{15}\text{R}^{16}$ ,  $-\text{N}(\text{R}^{16})\text{SONH}_2$ ,  $-\text{N}(\text{R}^{16})\text{SONR}^{15}\text{R}^{16}$ ,  $-\text{N}(\text{R}^{16})\text{SO}_2\text{NH}_2$ ,  $-\text{N}(\text{R}^{16})\text{SO}_2\text{NR}^{15}\text{R}^{16}$ , or  $-\text{N}(\text{R}^{16})\text{Cyc}^1$  [where  $\text{Cyc}^1$  is an optionally substituted  $\text{C}_{3-7}$  monocyclic carbocyclic group optionally containing one or more -O- or -S- atoms or  $-\text{N}(\text{R}^{14})-$ ,  $-\text{C}(\text{O})-$ ,  $-\text{C}(\text{S})-$ ,  $-\text{S}(\text{O})-$  or  $-\text{S}(\text{O}_2)-$  groups].

25 Cyclic amino substituents which may be present on  $\text{R}^2$ ,  $\text{R}^3$ ,  $\text{R}^6$  and/or  $\text{R}^{10}$  aliphatic or heteroaliphatic groups include groups of formula  $-\text{NHet}^1$ , where  $-\text{NHet}^1$  is an optionally substituted  $\text{C}_{3-7}$  cyclic amino group optionally containing one or more other heteroatoms or heteroatom containing groups selected from -O- or -S- atoms  $-\text{N}(\text{R}^{14})-$ ,  $-\text{C}(\text{O})-$ ,  $-\text{C}(\text{S})-$ ,  $-\text{S}(\text{O})-$  or  $-\text{S}(\text{O}_2)-$  groups.

Particular examples of amino, substituted amino and cyclic amino groups include  $-\text{NH}_2$ , methylamino, ethylamino, dimethylamino, diethylamino,  $-\text{NHCyc}^1$  where  $\text{Cyc}^1$  is an optionally substituted cyclopentyl, cyclohexyl, pyrrolidinyl, imidazolidinyl, pyrazolidinyl, piperidinyl, morpholinyl,

piperazinyl or thiomorpholinyl group, or -NHet<sup>1</sup> where -NHet<sup>1</sup> is an optionally substituted pyrrolidinyl, imidazolidinyl, pyrazolidinyl, piperidinyl, morpholinyl, piperazinyl or thiomorpholinyl group. Optional substituents which may be present on these groups and substituted and cyclic amino groups in general include one, two or three halogen atoms, e.g. fluorine, chlorine, bromine or iodine atoms, or C<sub>1-4</sub>alkyl, e.g. methyl or ethyl, hydroxyl, C<sub>1-4</sub>alkoxy, e.g. methoxy or ethoxy or pyridyl groups.

Optional heteroaromatic substituents which may be present on the aliphatic or heteroaliphatic groups represented by R<sup>2</sup>, R<sup>3</sup>, R<sup>6</sup> and/or R<sup>10</sup> include those heteroaromatic groups described below in relation to R<sup>2</sup>, R<sup>3</sup>, R<sup>6</sup> and R<sup>10</sup>.

When R<sup>2</sup>, R<sup>3</sup>, R<sup>6</sup> and/or R<sup>10</sup> is present in compounds of formula (1) as an optionally substituted cycloaliphatic group it may be an optionally substituted C<sub>3-10</sub> cycloaliphatic group. Particular examples include optionally substituted C<sub>3-10</sub>cycloalkyl, e.g. C<sub>3-7</sub>cycloalkyl, or C<sub>3-10</sub>cycloalkenyl e.g. C<sub>3-7</sub>cycloalkenyl groups.

Heteroaliphatic or heterocycloaliphatic groups represented by R<sup>2</sup>, R<sup>3</sup>, R<sup>6</sup> and/or R<sup>10</sup> include the aliphatic or cycloaliphatic groups just described for these substituents but with each group additionally containing one, two, three or four heteroatoms or heteroatom-containing groups represented by X<sup>2</sup>, where X<sup>2</sup> is as described above.

Particular examples of R<sup>2</sup>, R<sup>3</sup>, R<sup>6</sup> and/or R<sup>10</sup> cycloaliphatic and heterocycloaliphatic groups include optionally substituted cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, 2-cyclobuten-1-yl, 2-cyclopenten-1-yl, 3-cyclopenten-1-yl, 2,4-cyclopentadien-1-yl, 3,5-cyclohexadien-1-yl, tetrahydrofuranyl, pyrroline, e.g. 2- or 3-pyrrolinyl, pyrrolidinyl, dioxolanyl, e.g. 1,3-dioxolanyl, imidazolanyl, e.g. 2-imidazolanyl, imidazolidinyl, pyrazolanyl, e.g. 2-pyrazolanyl, pyrazolidinyl, pyranal, e.g. 2- or 4-pyranal, piperidinyl, 1,4-dioxanyl, morpholinyl, 1,4-dithianyl, thiomorpholinyl, piperazinyl, 1,3,5-trithianyl, oxazinyl, e.g. 2H-1,3-, 6H-1,3-, 6H-1,2-, 2H-1,2- or 4H-1,4- oxazinyl, 1,2,5-oxathiazinyl,

isoxaziny, oxathiaziny, e.g. 1,2,5 or 1,2,6-oxathiaziny, or 1,3,5-oxadiaziny groups.

Optional substituents which may be present on R<sup>2</sup>, R<sup>3</sup>, R<sup>6</sup> and/or R<sup>10</sup> cycloaliphatic and heterocycloaliphatic groups include those optional substituents described above for R<sup>6</sup> when it is an aliphatic group. The heterocycloaliphatic groups may be attached to the remainder of the molecule of formula (1) through any appropriate ring carbon or heteroatom.

10

When R<sup>2</sup>, R<sup>3</sup>, R<sup>6</sup> and/or R<sup>10</sup> is present as an aromatic group in compounds of formula (1) it may be for example an optionally substituted monocyclic or bicyclic fused ring C<sub>6-12</sub> aromatic group, such as an optionally substituted phenyl, 1- or 2-naphthyl, 1- or 2-tetrahydronaphthyl, indanyl or indenyl group.

15

Heteroaromatic groups represented by R<sup>2</sup>, R<sup>3</sup>, R<sup>6</sup> and/or R<sup>10</sup> include optionally substituted C<sub>1-9</sub> heteroaromatic groups containing for example one, two, three or four heteroatoms selected from oxygen, sulphur or nitrogen atoms. In general, the heteroaromatic groups may be for example monocyclic or bicyclic fused ring heteroaromatic groups. Monocyclic heteroaromatic groups include for example five- or six-membered heteroaromatic groups containing one, two, three or four heteroatoms selected from oxygen, sulphur or nitrogen atoms. Bicyclic heteroaromatic groups include for example nine- to thirteen-membered fused-ring heteroaromatic groups containing one, two or more heteroatoms selected from oxygen, sulphur or nitrogen atoms.

20

25

Examples of heteroaromatic groups represented by R<sup>2</sup>, R<sup>3</sup>, R<sup>6</sup> and/or R<sup>10</sup> include optionally substituted pyrrolyl, furyl, thienyl, imidazolyl, N-methylimidazolyl, N-ethyl-imidazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyrazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl, 1,3,4-thiadiazole, pyridyl, pyrimidinyl, pyridazinyl, pyrazinyl, 1,3,5-triazinyl, 1,2,4-triazinyl, 1,2,3-triazinyl, benzofuryl, [2,3-dihydro]benzofuryl, isobenzofuryl, benzothienyl, benzotriazolyl, isobenzothienyl, indolyl, isoindolyl,

30

35

benzimidazolyl, imidazo[1,2-a]pyridyl, benzothiazolyl, benzoxazolyl, benzopyranyl, [3,4-dihydro]benzopyranyl, quinazolinyl, naphthyridinyl, pyrido[3,4-b]pyridyl, pyrido[3,2-b]pyridyl, pyrido[4,3-b]pyridyl, quinolinyl, isoquinolinyl, tetrazolyl, 5,6,7,8-tetrahydroquinolinyl, 5,6,7,8-tetrahydro-  
 5 isoquinolinyl, and imidyl, e.g. succinimidyl, phthalimidyl, or naphthalimidyl such as 1,8-naphthalimidyl.

Optional substituents which may be present on any of the just described aromatic or heteroaromatic groups include one, two, three or more  
 10 substituents, each represented by the group  $R^{17}$  as more particularly defined below in relation to the phenyl substituent  $R^{11}$ .

Substituted amino groups represented by the groups  $R^1$ ,  $R^2$  and/or  $R^3$  in compounds of formula (1) include for example the groups  $-NR^{15}R^{16}$ ,  
 15  $-N(R^{16})COR^{15}$ ,  $-N(R^{16})CSR^{15}$ ,  $-N(R^{16})SOR^{15}$ ,  $-N(R^{16})SO_2R^{15}$ ,  $-N(R^{16})CONH_2$ ,  $-N(R^{16})CONR^{15}R^{16}$ ,  $-N(R^{16})C(O)OR^{15}$ ,  $-N(R^{16})C(NH)NH_2$ ,  $-N(R^{16})C(NH)NR^{15}R^{16}$ ,  $-N(R^{16})CSNH_2$ ,  $-N(R^{16})CSNR^{15}R^{16}$ ,  $-N(R^{16})SONH_2$ ,  $-N(R^{16})SONR^{15}R^{16}$ ,  $-N(R^{16})SO_2NH_2$ ,  $-N(R^{16})SO_2NR^{15}R^{16}$ ,  $-N(R^{16})Cyc^1$  where  $R^{15}$ ,  $R^{16}$   
 20 and  $Cyc^1$  are as defined above.

Halogen atoms represented by the group  $R^5$  in compounds of the invention include fluorine, chlorine, bromine and iodine atoms. Alkynyl groups represented by  $R^5$  include  $-CCH$  and  $CCCH_3$  groups.

25

The group  $R^{11}$  in compounds of formula (1) may be a phenyl or substituted phenyl group. The substituted phenyl group may contain one, two, three or more substituents, each represented by the group  $R^{17}$ .

30 The substituent  $R^{17}$  may be selected from an atom or group  $R^{18}$  or  $-Alk(R^{18})_m$ , where  $R^{18}$  is a halogen atom, or an amino ( $-NH_2$ ),  $-NHR^{19}$  [where  $R^{19}$  is an  $-Alk(R^{18})_m$ , heterocycloaliphatic,  $-Alk$ -heterocycloaliphatic, aryl or heteroaryl group],  $-N(R^{19})_2$  [where each  $R^{19}$  group is the same or different], nitro, cyano, hydroxyl ( $-OH$ ),  $-OR^{19}$ , formyl, carboxyl ( $-CO_2H$ ), esterified carboxyl, thiol ( $-SH$ ),  $-SR^{19}$ ,  $-COR^{19}$ ,  $-CSR^{19}$ ,  $-SO_3H$ ,  
 35  $-SO_2R^{19}$ ,  $-SO_2NH_2$ ,  $-SO_2NHR^{19}$ ,  $SO_2N[R^{19}]_2$ ,  $-CONH_2$ ,  $-CSNH_2$ ,



-CONHR<sup>19</sup>, -CSNHR<sup>19</sup>, -CON[R<sup>19</sup>]<sub>2</sub>, -CSN[R<sup>19</sup>]<sub>2</sub>, -N(R<sup>14</sup>)SO<sub>2</sub>H [where R<sup>14</sup> is as defined above], -N(R<sup>14</sup>)SO<sub>2</sub>R<sup>19</sup>, -N[SO<sub>2</sub>R<sup>19</sup>]<sub>2</sub>, -N(R<sup>14</sup>)SO<sub>2</sub>NH<sub>2</sub>, -N(R<sup>14</sup>)SO<sub>2</sub>NHR<sup>19</sup>, -N(R<sup>14</sup>)SO<sub>2</sub>N[R<sup>19</sup>]<sub>2</sub>, -N(R<sup>14</sup>)COR<sup>19</sup>, -N(R<sup>14</sup>)CONH<sub>2</sub>, -N(R<sup>14</sup>)CONHR<sup>19</sup>, -N(R<sup>14</sup>)CON[R<sup>19</sup>]<sub>2</sub>, -N(R<sup>14</sup>)CSR<sup>19</sup>, -N(R<sup>14</sup>)CSNH<sub>2</sub>,  
 5 -N(R<sup>14</sup>)CSNHR<sup>19</sup>, -N(R<sup>14</sup>)CSN[R<sup>19</sup>]<sub>2</sub>, -N(R<sup>14</sup>)C(O)OR<sup>19</sup>, or an optionally substituted cycloaliphatic, heterocycloaliphatic, aryl or heteroaryl group; Alk is a straight or branched C<sub>1-6</sub> alkylene, C<sub>2-6</sub> alkenylene or C<sub>2-6</sub> alkynylene chain, optionally interrupted by one, two or three -O- or -S- atoms or S(O)-, -S(O)<sub>2</sub>- or -N(R<sup>14</sup>)- groups; and m is zero or an integer 1,  
 10 2 or 3.

When in the group -Alk(R<sup>18</sup>)<sub>m</sub> m is an integer 1, 2 or 3, it is to be understood that the substituent or substituents R<sup>18</sup> may be present on any suitable carbon atom in -Alk. Where more than one R<sup>18</sup> substituent is  
 15 present these may be the same or different and may be present on the same or different atom in -Alk or in R<sup>17</sup> as appropriate. Thus for example, R<sup>17</sup> may represent a -CH(R<sup>18</sup>)<sub>2</sub> group, such as a -CH(OH)Ar group where Ar is an aryl or heteroaryl group as defined below. Clearly, when m is zero and no substituent R<sup>18</sup> is present the alkylene, alkenylene or alkynylene chain represented by Alk becomes an alkyl, alkenyl or alkynyl group.  
 20

When R<sup>18</sup> is a halogen atom it may be for example a fluorine, chlorine, bromine, or iodine atom.

25 Esterified carboxyl groups represented by the group R<sup>18</sup> include groups of formula -CO<sub>2</sub>Alk<sup>1</sup> wherein Alk<sup>1</sup> is a straight or branched, optionally substituted C<sub>1-8</sub> alkyl group such as a methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, s-butyl or t-butyl group; a C<sub>6-12</sub>arylC<sub>1-8</sub>alkyl group such as an optionally substituted benzyl, phenylethyl, phenylpropyl, 1-naphthyl-  
 30 methyl or 2-naphthylmethyl group; a C<sub>6-12</sub>aryl group such as an optionally substituted phenyl, 1-naphthyl or 2-naphthyl group; a C<sub>6-12</sub>aryloxyC<sub>1-8</sub>alkyl group such as an optionally substituted phenyloxymethyl, phenyloxyethyl, 1-naphthyloxymethyl, or 2-naphthyloxymethyl group; an optionally substituted C<sub>1-8</sub>alkanoyloxyC<sub>1-8</sub>alkyl group, such as a pivaloyloxymethyl, propionyloxyethyl or propionyloxypropyl group; or a C<sub>6-12</sub>aroxyloxyC<sub>1-8</sub>alkyl  
 35 group such as an optionally substituted benzoyloxyethyl or benzoyl-

oxypropyl group. Optional substituents present on the Alk<sup>1</sup> group include R<sup>18</sup> substituents described above.

When Alk is present in or as a substituent R<sup>17</sup> it may be for example a  
5 methylene, ethylene, n-propylene, i-propylene, n-butylene, i-butylene,  
s-butylene, t-butylene, ethenylene, 2-propenylene, 2-butenylene,  
3-butenylene, ethynylene, 2-propynylene, 2-butyneylene or 3-butyneylene  
chain, optionally interrupted by one, two, or three -O- or -S-, atoms or  
-S(O)-, -S(O)<sub>2</sub>- or -N(R<sup>14</sup>)- groups.

10

When R<sup>18</sup> is present in compounds of formula (1) as an optionally  
substituted cycloaliphatic group it may be an optionally substituted C<sub>3-10</sub>  
cycloaliphatic group. Particular examples include optionally substituted  
C<sub>3-10</sub>cycloalkyl, e.g. C<sub>3-7</sub>cycloalkyl, or C<sub>3-10</sub>cycloalkenyl e.g. C<sub>3-7</sub>  
15 cycloalkenyl groups.

15

Heterocycloaliphatic groups represented by R<sup>19</sup> and when present R<sup>19</sup>  
include the cycloaliphatic groups just described for R<sup>18</sup> but with each  
group additionally containing one, two, three or four heteroatoms or  
20 heteroatom-containing groups selected from -O- or -S- atoms or -N(R<sup>14</sup>)-,  
-C(O)-, -C(S)-, -S(O)- or -S(O)<sub>2</sub>- groups.

20

Particular examples of R<sup>18</sup> cycloaliphatic and R<sup>18</sup> or R<sup>19</sup> heterocyclo-  
aliphatic groups include optionally substituted cyclopropyl, cyclobutyl,  
25 cyclopentyl, cyclohexyl, cycloheptyl, 2-cyclobuten-1-yl, 2-cyclopenten-1-yl,  
3-cyclopenten-1-yl, 2,4-cyclopentadien-1-yl, 3,5-cyclohexadien-1-yl,  
tetrahydrofuranyl, pyrroline, e.g. 2- or 3-pyrrolinyl, pyrrolidinyl, dioxolanyl,  
e.g. 1,3-dioxolanyl, imidazolanyl, e.g. 2-imidazolanyl, imidazolidinyl,  
pyrazolanyl, e.g. 2-pyrazolanyl, pyrazolidinyl, pyranal, e.g. 2- or 4-pyranal,  
30 piperidinyl, 1,4-dioxanyl, morpholinyl, 1,4-dithianyl, thiomorpholinyl,  
piperazinyl, 1,3,5-trithianyl, oxazinyl, e.g. 2H-1,3-, 6H-1,3-, 6H-1,2-, 2H-  
1,2- or 4H-1,4- oxazinyl, 1,2,5-oxathiazinyl, isoxazinyl, oxathiazinyl, e.g.  
1,2,5 or 1,2,6-oxathiazinyl, or 1,3,5-oxadiazinyl groups.

30

35 Optional substituents which may be present on R<sup>18</sup> cycloaliphatic and R<sup>18</sup>  
or R<sup>19</sup> heterocycloaliphatic groups include one, two, three or more

substituents selected from halogen atoms, e.g. fluorine, chlorine, bromine or iodine atoms, or hydroxyl, C<sub>1-6</sub>alkoxy, e.g. methoxy or ethoxy, thiol, C<sub>1-6</sub>alkylthio, e.g. methylthio or ethylthio, hydroxy, C<sub>1-6</sub>alkyl, e.g. hydroxymethyl, hydroxyethyl, -CN, -NO<sub>2</sub>, -NHR<sup>14</sup> or -N(R<sup>14</sup>)<sub>2</sub> groups.

5

Aryl and heteroaryl groups represented by the group R<sup>18</sup> or Ar include for example optionally substituted monocyclic or bicyclic C<sub>6-12</sub> aromatic groups, e.g. phenyl groups, or C<sub>1-9</sub> heteroaromatic groups such as those described above in relation to the group R<sup>6</sup>. Optional substituents which  
10 may be present on these groups include one, two or three R<sup>18a</sup> atoms or groups described below.

Particularly useful atoms or groups represented by R<sup>18</sup>, -Alk(R<sup>18</sup>)<sub>m</sub> or R<sup>18a</sup> as appropriate include fluorine, chlorine, bromine or iodine atoms, or C<sub>1-6</sub>alkyl, e.g. methyl or ethyl, C<sub>1-6</sub>alkylamino, e.g. methylamino or ethylamino, C<sub>1-6</sub>hydroxyalkyl, e.g. hydroxymethyl or hydroxyethyl, C<sub>1-6</sub>alkylthiol e.g. methylthiol or ethylthiol, C<sub>1-6</sub>alkoxy, e.g. methoxy or ethoxy, C<sub>5-7</sub>cycloalkoxy, e.g. cyclopentyloxy, haloC<sub>1-6</sub>alkyl, e.g. trifluoromethyl, C<sub>1-6</sub>alkylamino, e.g. methylamino or ethylamino, amino (-NH<sub>2</sub>), aminoC<sub>1-6</sub>alkyl, e.g. aminomethyl or aminoethyl, C<sub>1-6</sub>dialkylamino, e.g. dimethylamino or diethylamino, imido, such as phthalimido or naphthalimido, e.g. 1,8-naphthalimido, 1,1,3-trioxo-benzo[d]-thiazolidino, nitro, cyano, hydroxyl (-OH), formyl [HC(O)-], carboxyl (-CO<sub>2</sub>H), -CO<sub>2</sub>Alk<sup>1</sup> [where Alk<sup>1</sup> is as defined above], C<sub>1-6</sub>alkanoyl e.g. acetyl, thiol  
25 (-SH), thioC<sub>1-6</sub>alkyl, e.g. thiomethyl or thioethyl, -SC(NH<sub>2</sub><sup>+</sup>)NH<sub>2</sub>, sulphonyl (-SO<sub>3</sub>H), C<sub>1-6</sub>alkylsulphonyl, e.g. methylsulphonyl, aminosulphonyl (-SO<sub>2</sub>NH<sub>2</sub>), C<sub>1-6</sub>alkylaminosulphonyl, e.g. methylaminosulphonyl or ethylaminosulphonyl, C<sub>1-6</sub>dialkylaminosulphonyl, e.g. dimethylaminosulphonyl or diethylaminosulphonyl, phenylaminosulphonyl, carboxamido  
30 (-CONH<sub>2</sub>), C<sub>1-6</sub>alkylaminocarbonyl, e.g. methylaminocarbonyl or ethylaminocarbonyl, C<sub>1-6</sub>dialkylaminocarbonyl, e.g. dimethylaminocarbonyl or diethylaminocarbonyl, sulphonylamino (-NH<sub>2</sub>SO<sub>2</sub>H), C<sub>1-6</sub>alkylsulphonylamino, e.g. methylsulphonylamino or ethylsulphonylamino, C<sub>1-6</sub>dialkylsulphonylamino, e.g. dimethylsulphonylamino or diethylsulphonylamino,  
35 optionally substituted phenylsulphonylamino, e.g. 2-, 3- or 4- substituted phenylsulphonylamino such as 2-nitrophenylsulphonylamino, amino-

sulphonylamino ( $-\text{NHSO}_2\text{NH}_2$ ),  $\text{C}_{1-6}$ alkylaminosulphonylamino, e.g. methylaminosulphonylamino or ethylaminosulphonylamino,  $\text{C}_{1-6}$ dialkylaminosulphonylamino, e.g. dimethylaminosulphonylamino or diethylaminosulphonylamino, phenylaminosulphonylamino, aminocarbonylamino,  
 5  $\text{C}_{1-6}$ alkylaminocarbonylamino e.g. methylaminocarbonylamino or ethylaminocarbonylamino,  $\text{C}_{1-6}$ dialkylaminocarbonylamino, e.g. dimethylaminocarbonylamino or diethylaminocarbonylamino, phenylaminocarbonylamino,  $\text{C}_{1-6}$ alkanoylamino, e.g. acetylamino, optionally substituted phenylcarbonylamino,  $\text{C}_{1-6}$ alkanoylamino $\text{C}_{1-6}$ alkyl, e.g. acetylaminomethyl,  $\text{C}_{1-6}$   
 10 alkoxycarbonylamino, e.g. methoxycarbonylamino, ethoxycarbonylamino or t-butoxycarbonylamino, optionally substituted hetero $\text{C}_{3-6}$ cycloalkyl, e.g. piperidinyl, piperazinyl, 4-( $\text{C}_{1-6}$ alkyl)piperazinyl, e.g. 4-methylpiperazinyl, homopiperazinyl, or morpholinyl, optionally substituted hetero $\text{C}_{3-6}$ cycloalkyl $\text{C}_{1-6}$ alkyl, e.g. piperidinyl $\text{C}_{1-6}$ alkyl, piperazinyl $\text{C}_{1-6}$ alkyl, 4-( $\text{C}_{1-6}$ alkyl)piperazinyl $\text{C}_{1-6}$ alkyl, e.g. 4-methylpiperazinylmethyl, or morpholinyl- $\text{C}_{1-6}$ alkyl, optionally substituted hetero $\text{C}_{3-6}$ alkyl $\text{C}_{1-6}$ alkylamino, optionally substituted hetero $\text{C}_{3-6}$ cycloalkylamino, tetrazolyl, optionally substituted imidazolyl $\text{C}_{1-6}$ alkyl, optionally substituted phenylamino, optionally substituted benzylamino, optionally substituted benzyloxy, or optionally  
 20 substituted pyridylmethylamino group.

Where desired, two  $\text{R}^{18}$  or  $-\text{Alk}(\text{R}^{18})_m$  or  $\text{R}^{18a}$  substituents may be linked together to form a cyclic group such as a cyclic ether, e.g. a  $\text{C}_{2-6}$ alkylenedioxy group such as ethylenedioxy.

25

It will be appreciated that where two or more  $\text{R}^{18}$ ,  $-\text{Alk}(\text{R}^{18})_m$  or  $\text{R}^{18a}$  substituents are present, these need not necessarily be the same atoms and/or groups.

30 Especially useful  $\text{R}^{18}$ ,  $-\text{Alk}(\text{R}^{18})_m$  or  $\text{R}^{18a}$  substituents include for example fluorine, chlorine, bromine or iodine atoms, or a methylamino, ethylamino, hydroxymethyl, hydroxyethyl, methylthiol, ethylthiol, methoxy, ethoxy, n-propoxy, 2-hydroxyethoxy, 3-hydroxypropoxy, 4-hydroxybutoxy, 2-aminoethoxy, 3-aminopropoxy, 2-(methylamino)ethoxy, 2-(dimethylamino)ethoxy,  
 35 3-(dimethylamino)propoxy, cyclopentyloxy, cyclohexyl, cyclohexylamino, 2-hydroxycyclohexylamino, trifluoromethyl, trifluoromethoxy, methylamino,

ethylamino, amino (-NH)<sub>2</sub>, aminomethyl, aminoethyl, dimethylamino, diethylamino, ethyl(methyl)amino, propyl(methyl)amino, 2-hydroxyethylamino, 3-hydroxypropylamino, 4-hydroxybutylamino, 2-aminoethylamino, 3-aminopropylamino, 4-aminobutylamino, 2-(methylamino)ethylamino, 2-(ethylamino)ethylamino, 2-(i-propylamino)ethylamino, 3-(i-propylamino)propylamino, 2-(dimethylamino)ethylamino, 3-(dimethylamino)propylamino, 2-(diethylamino)ethylamino, 3-(diethylamino)propylamino, 2-(methylamino)-ethyl(methyl)amino, 3-(methylamino)propyl(methyl)amino, 2-(dimethylamino)ethyl(methyl)amino, 2-(dimethylamino)ethyl(ethyl)amino, nitro, cyano, hydroxyl (-OH), formyl [HC(O)-], carboxyl (-CO<sub>2</sub>H), -CH<sub>2</sub>CO<sub>2</sub>H, -OCH<sub>2</sub>CO<sub>2</sub>H, -CO<sub>2</sub>CH<sub>3</sub>, -CO<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>, -CH<sub>2</sub>CO<sub>2</sub>CH<sub>3</sub>, -CH<sub>2</sub>CO<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>, -CH<sub>2</sub>CO<sub>2</sub>CH<sub>2</sub>phenyl, t-butoxycarbonylmethoxy, acetyl, phenacetyl, thio (-SH), thiomethyl, thioethyl, -SC(NH)NH<sub>2</sub>, sulphonyl (-SO<sub>2</sub>H), methylsulphonyl, methylaminosulphonyl, ethylaminosulphonyl, dimethylaminosulphonyl, diethylaminosulphonyl, carboxamido (-CONH<sub>2</sub>), methylaminocarbonyl, ethylaminocarbonyl, dimethylaminocarbonyl, diethylaminocarbonyl, methylaminocarbonylmethyl, -NHC(S)NH<sub>2</sub>, sulphonylamino (-NHSO<sub>2</sub>H), methylsulphonylamino, ethylsulphonylamino, dimethylsulphonylamino, diethylsulphonylamino, sulphonylamino (-NHSO<sub>2</sub>NH<sub>2</sub>), methylaminosulphonylamino, ethylaminosulphonylamino, dimethylaminosulphonylamino, diethylaminosulphonylamino, methylaminocarbonylamino, ethylaminocarbonylamino, dimethylaminocarbonylamino, diethylaminocarbonylamino, acetylamino, phenylcarbonylamino, aminomethylcarbonylamino, acetylaminomethyl, methoxycarbonylamino, ethoxycarbonylamino, t-butoxycarbonylamino, pyrrolidinyl, piperidinyl, piperazinyl, 4-methylpiperazinyl, homopiperazinyl, morpholinyl, pyrrolidinylC<sub>1-6</sub>alkyl, piperidinylC<sub>1-6</sub>alkyl, piperazinylC<sub>1-6</sub>alkyl, 4-(C<sub>1-6</sub>alkyl)piperazinylC<sub>1-6</sub>alkyl, morpholinylC<sub>1-6</sub>alkyl, 2-pyrrolidinyethylamino, 2-(1-methylpyrrolidinyl)ethylamino, 1-ethylpyrrolidinylmethylamino, piperidinylamino, 1-benzylpiperidinylamino, imidazolylmethyl, imidazolylethyl, 4-(methoxy)phenylamino, 4-(3-hydroxypropyl)phenylamino, benzylamino, benzyloxy or pyridylmethylamino group.

When X<sup>1</sup> is present in compounds of the invention as a -(R<sup>12</sup>)(R<sup>13</sup>)- group it may be for example a -CH<sub>2</sub>- or -C(R<sup>12</sup>)(R<sup>13</sup>)- group in which R<sup>12</sup> and/or R<sup>13</sup> is each a halogen atom such as a fluorine or chlorine atom or a

hydroxy, C<sub>1-6</sub>alkyl e.g. methyl, ethyl or i-propyl, or C<sub>1-6</sub>haloalkyl, e.g. trihalomethyl such as a trifluoromethyl group. Particular examples of such -C(R<sup>12</sup>)(R<sup>13</sup>)- groups include -CHF-, -CH(CH<sub>3</sub>)-, -C(OH)(CF<sub>3</sub>)- and -CH(CF<sub>3</sub>)- groups.

5

The presence of certain substituents in the compounds of formula (1) may enable salts of the compounds to be formed. Suitable salts include pharmaceutically acceptable salts, for example acid addition salts derived from inorganic or organic acids, and salts derived from inorganic and organic bases.

10

Acid addition salts include hydrochlorides, hydrobromides, hydroiodides, alkylsulphonates, e.g. methanesulphonates, ethanesulphonates, or isethionates, arylsulphonates, e.g. p-toluenesulphonates, besylates or napsylates, phosphates, sulphates, hydrogen sulphates, acetates, trifluoroacetates, propionates, citrates, maleates, fumarates, malonates, succinates, lactates, oxalates, tartrates and benzoates.

15

Salts derived from inorganic or organic bases include alkali metal salts such as sodium or potassium salts, alkaline earth metal salts such as magnesium or calcium salts, and organic amine salts such as morpholine, piperidine, piperazine, dimethylamine or diethylamine salts.

20

Particularly useful salts of compounds according to the invention include pharmaceutically acceptable salts, especially acid addition pharmaceutically acceptable salts.

25

It will be appreciated that depending on the nature of the substituents R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup> and R<sup>4</sup> the compounds of formula (1) may exist as tautomers and/or geometrical isomers and/or may have one or more chiral centres so that enantiomers or diastereomers may exist. It is to be understood that the invention extends to all such tautomers and isomers of the compounds of formula (1), and to mixtures thereof, including racemates.

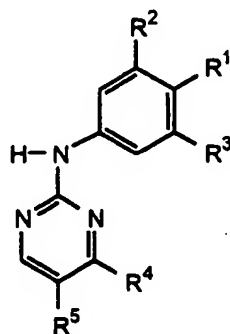
30

In the compounds according to the invention the group R<sup>4</sup> is preferably a group X<sup>1</sup>R<sup>11</sup> in which X<sup>1</sup> is a covalent bond.

35

The group  $R^5$  in compounds of the invention is in particular a bromine or, especially a chlorine atom.

- 5 A particularly useful group of compounds according to the invention has the formula (1a):



(1a)

- 10 wherein  $R^1$ ,  $R^2$ ,  $R^3$ ,  $R^4$  and  $R^5$  are as defined for formula (1).

One particular class of compounds of formulae (1) and (1a) is that wherein one or both of  $R^2$  and  $R^3$  is a hydrogen atom. Compounds in which  $R^2$  and  $R^3$  is each a hydrogen atom are especially useful.

15

- In compounds of this class  $R^1$  is in particular a group  $-(Alk^2)_pNH_2$  (where  $Alk^2$  is as defined above for  $Alk$  and  $p$  is zero or an integer 1),  $-(Alk^2)_pNR^{15}R^{16}$  (where  $R^{15}$  and  $R^{16}$  are as defined above),  $-(Alk^2)_pNHet^2$  (where  $-NHet^2$  is as defined above for  $NHet^1$ ),  $-(Alk^2)_pOH$ ,  
 20 and  $-(Alk^2)_pAr$  (where  $Ar$  is a nitrogen-containing heteroaromatic group as defined above). Especially useful  $R^1$  substituents include  $-Alk^2NH_2$ , particularly  $-(CH_2)_2NH_2$  and  $-C(CH_3)_2NH_2$ ,  $-Alk^2NR^{15}R^{16}$ , particularly  $-CH_2N(CH_2CH_3)_2$  and  $-(CH_2)_2NHC(CH_3)_3$ ,  $-(Alk^2)_pNHet^2$  where  $-NHet^2$  is an optionally substituted pyrrolidiny, piperidiny, piperaziny, morpholiny or thiomorpholiny group,  
 25  $-Alk^2OH$ , particularly  $-(CH_2)_2OH$  and  $-(Alk^2)_pAr$  where  $Ar$  is an optionally substituted imidazolyl or benzimidazolyl group. Optional substituents which may be present on these particular  $-NHet^2$  or

Ar groups include those generally and particularly described above in relation to the groups -NHet<sup>1</sup> and Ar.

- In general in compounds of formulae (1) or (1a) R<sup>4</sup> is preferably a group X<sup>1</sup>R<sup>11</sup> in which X<sup>1</sup> is a covalent bond and R<sup>11</sup> is a phenyl or, especially, a substituted phenyl group containing one, two or three R<sup>17</sup> substituents as defined herein. Particularly useful R<sup>17</sup> substituents include -(Alk<sup>2</sup>)<sub>p</sub>NH<sub>2</sub> substituents as just generally and particularly discussed for R<sup>1</sup>.
- 5
- 10 Particularly useful compounds according to the invention include:  
 4-[4-(1-Amino-1-methylethyl)phenyl]-5-chloro-N-[4-(2-hydroxyethyl)phenyl]pyrimidine-2-amine;  
 4-[4-(1-Amino-1-methylethyl)phenyl]-5-chloro-N-[3-(2-hydroxyethyl)phenyl]pyrimidine-2-amine;
- 15 4-[4-(1-Amino-1-methylethyl)phenyl]-5-chloro-N-[4-(1-imidazolyl)phenyl]pyrimidine-2-amine;  
 4-[4-(1-Amino-1-methylethyl)-3-fluorophenyl]-5-chloro-N-[4-(2-hydroxyethyl)phenyl]pyrimidine-2-amine;  
 4-[4-(1-Amino-1-methylethyl)phenyl]-5-chloro-N-[4-(2-(imidazol-1-yl)ethyl)phenyl]pyrimidine-2-amine;
- 20 4-[4-(1-Amino-1-methylethyl)phenyl]-5-chloro-N-[4-(2-(2-methylimidazol-1-yl)ethyl)phenyl]pyrimidine-2-amine;  
 4-[4-(1-Amino-1-methylethyl)phenyl]-5-chloro-N-[4-(2-(2-isopropylimidazol-1-yl)ethyl)phenyl]pyrimidine-2-amine;
- 25 4-[4-(1-Amino-1-methylethyl)phenyl]-5-chloro-N-[4-(2-thiomorpholinoethyl)phenyl]pyrimidine-2-amine;  
 4-[4-(1-Amino-1-methylethyl)phenyl]-5-chloro-N-[4-(2-(tertbutylamino)ethyl)phenyl]pyrimidine-2-amine;  
 4-[4-(1-Amino-1-methylethyl)phenyl]-5-chloro-N-[4-(2-(4-methylpiperazin-1-yl)ethyl)phenyl]pyrimidine-2-amine;
- 30 4-[4-(1-Amino-1-methylethyl)phenyl]-5-chloro-N-[4-(2-(4-ethylpiperazin-1-yl)ethyl)phenyl]pyrimidine-2-amine;  
 4-[4-(1-Amino-1-methylethyl)phenyl]-5-chloro-N-[4-(2-(3,5-dimethylpiperazin-1-yl)ethyl)phenyl]pyrimidine-2-amine;
- 35 4-[4-(1-Amino-1-methylethyl)phenyl]-5-chloro-N-[4-(2-(4-(pyrid-2-yl)piperazin-1-yl)ethyl)phenyl]pyrimidine-2-amine;



4-[4-(1-Amino-1-methylethyl)phenyl]-5-chloro-N-[4-(2-(pyrrolidin-1-yl)ethyl)phenyl]pyrimidine-2-amine;  
4-[4-(1-Amino-1-methylethyl)phenyl]-5-chloro-N-[4-(2-(piperidin-1-yl)ethyl)phenyl]pyrimidine-2-amine;  
5 (R)-4-[4-(1-Amino-1-methylethyl)phenyl]-5-chloro-N-[4-(2-(3-dimethylaminopyrrolidin-1-yl)ethyl)phenyl]pyrimidine-2-amine;  
and the salts, solvates, hydrates and N-oxides thereof.

10 Compounds according to the invention are potent and selective inhibitors of KDR and/or FGFR4 kinases as demonstrated by differential inhibition of these enzymes when compared to inhibition of other protein kinases such as EGFR kinase, p56<sup>lck</sup> kinase, ZAP-70 kinase, protein kinase C, Csk kinase and p59<sup>fyn</sup> kinase. The ability of the compounds to act in this way may be simply determined by employing tests such as those described in  
15 the Examples hereinafter.

The compounds according to the invention are thus of particular use in the prophylaxis and treatment of diseases in which inappropriate KDR kinase action plays a role, for example in disease states associated with  
20 angiogenesis. The compounds are then of use for example in the prophylaxis and treatment of cancer, prosiasis, rheumatoid arthritis, Kaposi's Sarcoma, ischemic heart disease, atherosclerosis and ocular diseases, such as diabetic retinopathy, involving retinal vessel proliferation and the invention is to be understood to extend to such uses and to the  
25 use of a compound of formula (1) in the preparation of a medicament for the prophylaxis and treatment of such diseases.

For the prophylaxis or treatment of disease the compounds according to the invention may be administered as pharmaceutical compositions, and  
30 according to a further aspect of the invention we provide a pharmaceutical composition which comprises a compound of formula (1) together with one or more pharmaceutically acceptable carriers, excipients or diluents.

Pharmaceutical compositions according to the invention may take a form  
35 suitable for oral, buccal, parenteral, nasal, topical or rectal administration, or a form suitable for administration by inhalation or insufflation.

For oral administration, the pharmaceutical compositions may take the form of, for example, tablets, lozenges or capsules prepared by conventional means with pharmaceutically acceptable excipients such as binding agents (e.g. pregelatinised maize starch, polyvinylpyrrolidone or hydroxypropyl methylcellulose); fillers (e.g. lactose, microcrystalline cellulose or calcium hydrogen phosphate); lubricants (e.g. magnesium stearate, talc or silica); disintegrants (e.g. potato starch or sodium glycollate); or wetting agents (e.g. sodium lauryl sulphate). The tablets may be coated by methods well known in the art. Liquid preparations for oral administration may take the form of, for example, solutions, syrups or suspensions, or they may be presented as a dry product for constitution with water or other suitable vehicle before use. Such liquid preparations may be prepared by conventional means with pharmaceutically acceptable additives such as suspending agents, emulsifying agents, non-aqueous vehicles and preservatives. The preparations may also contain buffer salts, flavouring, colouring and sweetening agents as appropriate.

Preparations for oral administration may be suitably formulated to give controlled release of the active compound.

For buccal administration the compositions may take the form of tablets or lozenges formulated in conventional manner.

The compounds for formula (1) may be formulated for parenteral administration by injection, including bolus injection or infusion or particle mediated injection. Formulations for injection may be presented in unit dosage form, e.g. in glass ampoule or multi dose containers, e.g. glass vials or a device containing a compressed gas such as helium for particle mediated administration. The compositions for bolus injection or infusion may take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilising, preserving and/or dispersing agents. Alternatively, the active ingredient may be in powder form for constitution with a suitable vehicle, e.g. sterile pyrogen-free water, before use. For

particle mediated administration the complex may be coated on particles such as microscopic gold particles.

5 In addition to the formulations described above, the compounds of formula (1) may also be formulated as a depot preparation. Such long acting formulations may be administered by implantation or by intramuscular injection. Where desired, the compounds according to the invention may also be conjugated to a polymer, e.g. a naturally occurring polymer such as albumin, to prolong the half life of the compounds when in use. Such  
10 conjugates may be formulated and delivered as described above.

For nasal administration or administration by inhalation, the compounds for use according to the present invention are conveniently delivered in the form of an aerosol spray presentation for pressurised packs or a nebuliser,  
15 with the use of suitable propellant, e.g. dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, carbon dioxide or other suitable gas or mixture of gases.

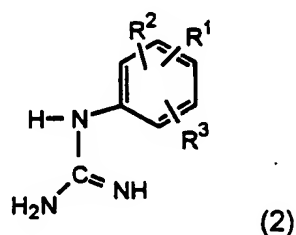
The compositions may, if desired, be presented in a pack or dispenser  
20 device which may contain one or more unit dosage forms containing the active ingredient. The pack or dispensing device may be accompanied by instructions for administration.

The quantity of a compound of the invention required for the prophylaxis or  
25 treatment of a particular condition will vary depending on the compound chosen, and the condition of the patient to be treated. In general, however, daily dosages may range from around 100ng/kg to 100mg/kg e.g. around 0.01mg/kg to 40mg/kg body weight for oral or buccal administration, from around 10ng/kg to 50mg/kg body weight for  
30 parenteral administration and around 0.05mg to around 1000mg e.g. around 0.5mg to around 1000mg for nasal administration or administration by inhalation or insufflation.

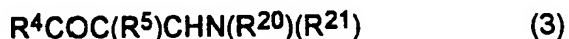
The compounds of the invention may be prepared by a number of  
35 processes as generally described below and more specifically in the Examples hereinafter. In the following process description, the symbols

R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup> and R<sup>5</sup> when used in the text or formulae depicted are to be understood to represent those groups described above in relation to formula (1) unless otherwise indicated. In the reactions described below, it may be necessary to protect reactive functional groups, for example hydroxy, amino, thio or carboxy groups, where these are desired in the final product, to avoid their unwanted participation in the reactions. Conventional protecting groups may be used in accordance with standard practice [see, for example, Green, T. W. in "Protective Groups in Organic Synthesis", John Wiley and Sons, 1991]. In some instances, deprotection may be the final step in the synthesis of a compound of formula (1) and the processes according to the invention described hereinafter are to be understood to extend to such removal of protecting groups.

Thus according to a further aspect of the invention, a compound of formula (1) may be prepared by reaction of a guanidine of formula (2):



or a salt thereof  
with an enaminone of formula (3):

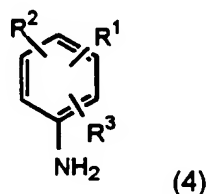


where R<sup>20</sup> and R<sup>21</sup>, which may be the same or different is each a C<sub>1-6</sub> Alkyl group.

The reaction may be performed in a solvent, for example a protic solvent such as an alcohol, e.g. ethanol, ethoxyethanol or propan-2-ol, optionally in the presence of a base e.g. an Alkali metal base, such as sodium hydroxide or potassium carbonate, at an elevated temperature, e.g. the reflux temperature.

Salts of the compounds of formula (2) include acid salts such as inorganic acid salts e.g. hydrochlorides or nitrates.

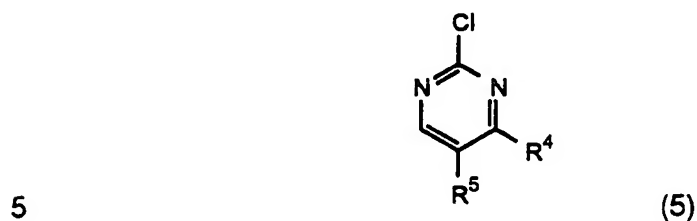
- 5 Intermediate guanidines of formula (2) may be prepared by reaction of the corresponding amine of formula (4):



- 10 with cyanamide at an elevated temperature. The reaction may be performed in a solvent such as ethanol at an elevated temperature, e.g. up to the reflux temperature. Where it is desired to obtain a salt of a guanidine of formula (2), the reaction may be performed in the presence of a concentrated acid, e.g. hydrochloric or nitric acid.
- 15 The amines of formula (4) are either known compounds or may be obtained by conventional procedures, for example by hydrogenation of the corresponding nitro derivatives using for example hydrogen in the presence of a metal catalyst in a suitable solvent, for example as more particularly described in the interconversion reactions discussed below.
- 20 The nitrobenzenes for this particular reaction are either known compounds or may be prepared using similar methods to those used for the preparation of the known compounds.

- 25 Intermediate enaminones of formula (3) are either known compounds or may be prepared by reaction of an acetyl derivative  $R^4COCH_2R^5$  with an acetal  $(R^{20})(R^{21})NCH(OR^{22})_2$  (where  $R^{22}$  is a  $C_{1-6}$ Alkyl group such as a methyl or ethyl group) at an elevated temperature. The starting materials for this reaction are either known compounds or may be prepared by methods analogous to those used for the preparation of the known compounds.
- 30

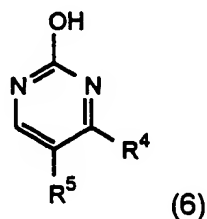
In another process according to the invention, a compound of formula (1) may be prepared by displacement of a chlorine atom in a pyrimidine of formula (5):



with an amine of formula (4)

10 The reaction may be performed at an elevated temperature, for example the reflux temperature, where necessary in the presence of a solvent, for example an alcohol, such as 2-ethoxyethanol or isopropanol, a cyclic ether, e.g. dioxane or a substituted amide such as dimethylformamide, optionally in the presence of a base, for example an organic amine such as pyridine.

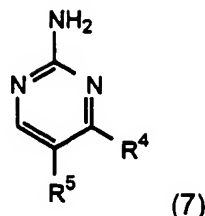
15 Intermediate pyrimidines of formula (5) may be obtained by reaction of a corresponding pyrimidine of formula (6):



20 with phosphorous oxychloride optionally in a solvent such as a substituted amide e.g. dimethylformamide at an elevated temperature, for example the reflux temperature.

25 Intermediates of formula (6) may be prepared from the corresponding amine of formula (7):

22



with sodium nitrite in an aqueous acid, e.g. aqueous sulphuric acid at around ambient temperature.

5

Amines of formula (7) may be prepared by reaction of an enaminone of formula (3) with a guanidine salt, e.g. guanidine carbonate, as described above for the preparation of compounds of formula (1).

- 10 Compounds of formula (1) may also be prepared by interconversion of other compounds of formula (1) and it is to be understood that the invention extends to such interconversion processes. Thus, for example, standard substitution approaches employing for example Alkylation, arylation, heteroarylation, acylation, thioacylation, sulphonylation, formylation or coupling reactions may be used to add new substituents to and/or extend existing substituents in compounds of formula (1). Alternatively existing substituents in compounds of formula (1) may be modified by for example oxidation, reduction or cleavage reactions to yield other compounds of formula (1).

20

The following describes in general terms a number of approaches which can be employed to modify existing phenyl and/or other aromatic or heteroaromatic groups in compounds of formula (1). It will be appreciated that each of these reactions will only be possible where an appropriate functional group exists in a compound of formula (1). Where desired, these reactions may also be performed on intermediates to compounds of formula (1).

25

- Thus, for example Alkylation, arylation or heteroarylation of a compound of formula (1) may be achieved by reaction of the compound with a reagent Alk, L or ArL, where Alk is an Alkyl group and Ar is an aryl or heteroaryl

30

group as defined above in relation to compounds of formula (1) and L is a leaving atom or group such as a halogen atom, e.g. a chlorine or bromine atom, or a sulphonyloxy group, e.g. an arylsulphonyloxy group such as a *p*-toluenesulphonyloxy group.

5

The Alkylation or arylation reaction may be carried out in the presence of a base, e.g. an inorganic base such as a carbonate, e.g. caesium or potassium carbonate, an Alkoxide, e.g. potassium *t*-butoxide, or a hydride, e.g. sodium hydride, in a dipolar aprotic solvent such as an amide, e.g. a substituted amide such as dimethylformamide or an ether, e.g. a cyclic ether such as tetrahydrofuran, at around 0°C to around 40°C.

10

In a variation of this process the leaving group L may be alternatively part of the compound of formula (1) and the reaction performed with an appropriate nucleophilic reagent at an elevated temperature. Particular nucleophilic reagents include cyclic amines, such as piperazine. Where appropriate the reaction may be performed in a solvent such as an aprotic solvent, e.g. a substituted amide such as dimethylformamide.

15

In another general example of an interconversion process, a compound of formula (1) may be acylated or thioacylated. The reaction may be performed for example with an acyl halide or anhydride in the presence of a base, such as a tertiary amine e.g. triethylamine in a solvent such as a halogenated hydrocarbon, e.g. dichloromethane at for example ambient temperature, or by reaction with a thioester in an inert solvent such as tetrahydrofuran at a low temperature such as around 0°C. The reaction is particularly suitable for use with compounds of formula (1) containing primary or secondary amino groups.

20

25

In a further general example of an interconversion process, a compound of formula (1) may be formylated, for example by reaction of the compound with a mixed anhydride  $\text{HCOOCOCH}_3$  or with a mixture of formic acid and acetic anhydride.

30

Compounds of formula (1) may be prepared in another general interconversion reaction by sulphonylation, for example by reaction of the

35



compound with a reagent  $\text{AlkS(O)}_2\text{L}$ , or  $\text{ArS(O)}_2\text{L}$  in the presence of a base, for example an inorganic base such as sodium hydride in a solvent such as an amide, e.g. a substituted amide such as dimethylformamide at for example ambient temperature. The reaction may in particular be

5 performed with compounds of formula (1) possessing a primary or secondary amino group.

In further examples of interconversion reactions according to the invention compounds of formula (1) may be prepared from other compounds of

10 formula (1) by modification of existing functional groups in the latter.

Thus in one example, ester groups  $-\text{CO}_2\text{Alk}^1$  in compounds of formula (1) may be converted to the corresponding acid  $[-\text{CO}_2\text{H}]$  by acid- or base-catalysed hydrolysis or by catalytic hydrogenation depending on the

15 nature of the group  $\text{Alk}^1$ . Acid- or base-catalysed hydrolysis may be achieved for example by treatment with an organic or inorganic acid, e.g. trifluoroacetic acid in an aqueous solvent or a mineral acid such as hydrochloric acid in a solvent such as dioxan or an Alkali metal hydroxide, e.g. lithium hydroxide in an aqueous alcohol, e.g. aqueous methanol.

20 Catalytic hydrogenation may be carried out using for example hydrogen in the presence of a metal catalyst, for example palladium on a support such as carbon in a solvent such as an ether, e.g. tetrahydrofuran or an alcohol, e.g. methanol.

25 In a second example,  $-\text{OAlk}$  [where  $\text{Alk}$  represents an Alkyl group such as a methyl group] groups in compounds of formula (1) may be cleaved to the corresponding alcohol  $-\text{OH}$  by reaction with boron tribromide in a solvent such as a halogenated hydrocarbon, e.g. dichloromethane at a low temperature, e.g. around  $-78^\circ\text{C}$ .

30 In another example, alcohol  $-\text{OH}$  groups in compounds of formula (1) may be converted to a corresponding  $-\text{OAlk}$  or  $-\text{OAr}$  group by coupling with a reagent  $\text{AlkOH}$  or  $\text{ArOH}$  in a solvent such as tetrahydrofuran in the presence of a phosphine, e.g. triphenylphosphine and an activator such as

35 diethyl-, diisopropyl-, or dimethylazodicarboxylate.

Aminosulphonylamino [-NHSO<sub>2</sub>NH<sub>2</sub>] groups in compounds of formula (1) may be obtained, in another example, by reaction of a corresponding amine [-NH<sub>2</sub>] with sulphamide in the presence of an organic base such as pyridine at an elevated temperature, e.g. the reflux temperature.

5

In another example of an interconversion process secondary amine groups in compounds of formula (1) may be Alkylated using an alcohol, e.g. ethanol and catalytic hydrogenation, employing for example hydrogen in the presence of a metal catalyst such as palladium on a support such as carbon.

10

In a further example, amine [-NH<sub>2</sub>] groups in compounds of formula (1) may be obtained by hydrolysis from a corresponding imide by reaction with hydrazine in a solvent such as an alcohol, e.g. ethanol at ambient temperature. In an alternative, amine groups may also be generated by reduction of the corresponding nitrile, for example using a reducing agent such as a borohydride, e.g. sodium borohydride or cerium trichloride.

15

In another example, a nitro [-NO<sub>2</sub>] group may be reduced to an amine [-NH<sub>2</sub>], for example by catalytic hydrogenation as just described, or by chemical reduction using for example a metal, e.g. tin or iron, in the presence of an acid such as hydrochloric acid.

20

N-oxides of compounds of formula (1) may be prepared for example by oxidation of the corresponding nitrogen base using an oxidising agent such as hydrogen peroxide in the presence of an acid such as acetic acid, at an elevated temperature, for example around 70°C to 80°C, or alternatively by reaction with a peracid such as peracetic acid in a solvent, e.g. dichloromethane, at ambient temperature.

25

30

Where salts of compounds of formula (1) are desired, these may be prepared by conventional means, for example by reaction of a compound of formula (1) with an appropriate acid or base in a suitable solvent or mixture of solvents, e.g. an organic solvent such as an ether, e.g. diethylether, or an alcohol, e.g. ethanol.

35

The following Examples illustrate the invention. In the Examples all  $^1\text{H}$ nmr were run at 300MHz unless specified otherwise. All temperatures are in  $^{\circ}\text{C}$ .

5 The following abbreviations are used:

THF - tetrahydrofuran;

DMF - dimethylformamide;

DMSO - dimethylsulphoxide;

TFA - trifluoroacetic acid;

10 **EXAMPLE 1**

**4-[4-(1-Amino-1-methylethyl)phenyl]-5-chloro-N-[4-(2-hydroxyethyl)phenyl]pyrimidine-2-amine**

A mixture of 4-[4-(1-tert-butoxycarbonylamino-1-methylethyl)phenyl]-2,5-dichloropyrimidine (1.53g, 4.0mmol) and 4-aminophenethyl alcohol (1.10g, 8.0mmol) in 2-ethoxyethanol (15ml) was heated to reflux for 18h. The  
15 reaction was cooled to room temperature, trifluoroacetic acid (2ml) added and the reaction stirred for 30min. Solvent was removed *in vacuo* and the residue partitioned between  $\text{CH}_2\text{Cl}_2$  (100ml) and saturated, aqueous  $\text{Na}_2\text{CO}_3$  (80ml). The aqueous layer was re-extracted with  $\text{CH}_2\text{Cl}_2$  (2 x  
20 80ml) and the combined  $\text{CH}_2\text{Cl}_2$  layer washed with aqueous  $\text{Na}_2\text{CO}_3$  (80ml), brine (80ml), dried ( $\text{MgSO}_4$ ) and concentrated *in vacuo*. The crude product was purified by column chromatography (silica, 10-15% methanol in  $\text{CH}_2\text{Cl}_2$ ) to give the title compound as a buff solid (1.30g) m.p. 162-163 $^{\circ}$ .  $\delta\text{H}$  ( $d^6\text{DMSO}$ ) 9.74 (1H, s), 8.55 (1H, s), 7.76 (2H, d,  $\downarrow$  8.5Hz),  
25 7.68 (2H, d,  $\downarrow$  8.5Hz), 7.62 (2H, d,  $\downarrow$  8.5Hz), 7.12 (2H, d,  $\downarrow$  8.5Hz), 4.57 (1H, bs), 3.55 (2H, m), 2.65 (2H, t,  $\downarrow$  7.2Hz), 1.41 (6H, s); MS (ESI) 383 ( $\text{MH}^+$ ,  $^{35}\text{Cl}$ , 100%).

The 4-[4-(1-tert-butoxycarbonylamino-1-methylethyl)phenyl]-2,5-dichloro pyrimidine used in the above process was prepared as follows:-

30 Cerium trichloride heptahydrate (22.47g, 60mmol) was dried in a flask under high vacuum (0.08 Torr) heated by an oil bath at 140-160 $^{\circ}$  for 4h. On cooling, nitrogen was introduced slowly into the flask and anhydrous THF (120ml) added to give a suspension of  $\text{CeCl}_3$  which was stirred for 16h at room temperature. The mixture was cooled to -65 $^{\circ}$ , methyl lithium  
35 (37.5ml of a 1.6M solution in diethylether, 60mmol) added dropwise and the mixture stirred for 0.5h. A solution of 4-bromobenzonitrile (3.64g,

- 20mmol) in THF (10ml) was added and the reaction stirred at  $-65^{\circ}$  for 3.5h before allowing the mixture to warm to  $-40^{\circ}$ . The reaction was quenched by the addition of 33% ammonium hydroxide (50ml) and then allowed to warm to room temperature. The resulting solids were removed by filtration through a pad of Celite® and were washed with ethyl acetate (3 x 100ml). The combined filtrates were washed with brine (20ml), the organic phase dried ( $\text{MgSO}_4$ ) and concentrated *in vacuo* to give 1-(4-bromophenyl)-1-methylethylamine as a yellow oil (4.01g). This product was heated at reflux in toluene (40ml) with di-tert-butyl dicarbonate (4.50g, 20.6mmol) for 1h. Solvent was removed *in vacuo* and the crude product recrystallised from hexane at  $-20^{\circ}$  to give tertbutyl N-{1-(4-bromophenyl)-1-methylethyl}carbamate as colourless crystals (3.47g) m.p.  $92-93^{\circ}$   $\delta\text{H}$  ( $\text{CDCl}_3$ ) 7.43 (2H, dt,  $\downarrow$  8.7, 2.7Hz), 7.26 (2H, dt,  $\downarrow$  8.8, 2.6Hz), 4.91 (1H, bs), 1.59 (6H, s), 1.36 (9H, bs).
- 15 A mixture of tert-butyl N-{1-(4-bromophenyl)-1-methylethyl}carbamate (1.57g, 5.0mmol), bis(pinacolato)diboron (1.40g, 5.5mmol), [1,1'-bis (diphenylphosphino)ferrocene]dichloropalladium(II) (123mg, 0.015mmol) and potassium acetate (1.47g, 15.0mmol) was dissolved in dry DMF (20ml) under nitrogen and heated to  $80^{\circ}$  for 5h. The reaction was then concentrated under reduced pressure, the resulting residue taken up in dichloromethane (80ml) and washed with water (1 x 80ml), then brine (1 x 80ml), dried ( $\text{MgSO}_4$ ) and again concentrated. The residue was subjected to column chromatography (silica gel; 15% ethyl acetate-hexane) to give tert-butyl N-{1-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-1-methylethyl}carbamate (1.55g) as a white solid m.p.  $140^{\circ}$ .  $\delta\text{H}$  ( $\text{CDCl}_3$ ) 7.77 (2H, d,  $\downarrow$  8.3Hz), 7.40 (2H, d,  $\downarrow$  8.4Hz), 1.63 (6H, s) and 1.34 (21H, s).
- 25 2M aqueous  $\text{Na}_2\text{CO}_3$  (4.7ml, 9.4mmol) was added to a solution of 2,4,5-trichloropyrimidine [Chesterfield, J.; McOmie, J. F. W.; Sayer, E. R.; J. Chem. Soc. (1955) 3478-3481] (1.18g, 6.44mmol), tert-butyl N-{1-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-1-methylethyl}carbamate (1.55g, 4.29mmol) and tetrakis(triphenylphosphine)palladium (O) (150mg, 0.13mmol) in ethyleneglycol dimethylether (20ml) under  $\text{N}_2$  and the mixture heated to reflux for 6h. The reaction was diluted with  $\text{H}_2\text{O}$  (30ml) and extracted with ethyl acetate (3 x 50ml), the combined ethyl acetate extracts were washed with brine (30ml), dried ( $\text{MgSO}_4$ ) and

concentrated *in vacuo*. The crude product was purified by column chromatography (SiO<sub>2</sub>, 15% ethyl acetate in hexane) to give 4-[4-(1-tert-butoxycarbonylamino-1-methylethyl)phenyl]-2,5-dichloropyrimidine as a white solid (1.34g).  $\delta$ H (d<sup>6</sup>DMSO) 8.62 (1H, s), 7.90 (2H, d,  $\downarrow$  8.6Hz), 7.54 (2H, dt,  $\downarrow$  8.7, 2.1Hz), 5.02 (1H, bs), 1.65 (6H, s) and 1.37 (9H, s).

### EXAMPLE 2

#### 4-[4-(1-Amino-1-methylethyl)phenyl]-5-chloro-N-[3-(2-hydroxyethyl)phenyl]pyrimidine-2-amine

The title compound was prepared from 4-[4-(1-tert-butoxycarbonylamino-1-methylethyl)phenyl]-2,5-dichloropyrimidine (1.50g, 6.55mmol) and 2-(3-aminophenyl)ethanol (942mg, 6.87mmol) following the method of Example 1. The crude product was purified by chromatography (Silica, 10% methanol in CH<sub>2</sub>Cl<sub>2</sub>) to give the title compound as a brown solid (600mg) m.p. 184-185°.  $\delta$ H (d<sup>6</sup>DMSO) 9.77 (1H, s), 8.57 (1H, s), 7.79 (2H, d,  $\downarrow$  8.4Hz), 7.68 (2H, d,  $\downarrow$  8.4Hz), 7.61-7.58 (2H, m), 7.17 (1H, t,  $\downarrow$  7.7Hz), 6.82 (1H, d,  $\downarrow$  7.4Hz), 4.62 (1H, bs), 3.60 (2H, t,  $\downarrow$  7.0Hz), 2.68 (2H, t,  $\downarrow$  7.1Hz), 2.07 (2H, bs), 1.41 (6H, s); MS (ESI) 383 (MH<sup>+</sup>, <sup>35</sup>Cl).

### EXAMPLE 3

#### 4-[4-(1-Amino-1-methylethyl)phenyl]-5-chloro-N-[4-(1-imidazolyl)phenyl]pyrimidine-2-amine

Sodium hydride (330mg, 8.25mmol) was added to a solution of 4-[4-(1-tert-butoxycarbonylamino-1-methylethyl)phenyl]-2,5-dichloropyrimidine (1.0g, 2.62mmol) and 1-(4-aminophenyl)-1H-imidazole (438mg, 2.75mmol) in dry THF (40ml) under N<sub>2</sub> and the mixture heated to reflux for 3h. The reaction was quenched with H<sub>2</sub>O (5ml), diluted with brine (50ml) and extracted with ethyl acetate (2 x 150ml). The ethyl acetate extracts were dried (MgSO<sub>4</sub>), concentrated *in vacuo* and the residue purified by column chromatography (silica; 2% ethyl acetate in CH<sub>2</sub>Cl<sub>2</sub>) to give 4-[4-(1-tert-butoxy carbonylamino-1-methylethyl)phenyl]-5-chloro-N-[4-(1-imidazolyl)-phenyl] pyrimidine-2-amine as a yellow solid (310mg) m.p. 218-220°. This intermediate was stirred at room temperature in trifluoroacetic acid (4ml) for 3h before concentrating the reaction *in vacuo*. The residue was diluted with 2M NaOH (aq) (50ml) and extracted with CH<sub>2</sub>Cl<sub>2</sub>-ethanol (20:1) (3 x 50ml), the extracts dried (MgSO<sub>4</sub>) and concentrated *in vacuo*. Trituration

of the resultant solid with diethylether-ethyl acetate (4:1) gave the title compound as a pale yellow solid (175mg) m.p. 199-201°.  $\delta$ H (d<sup>6</sup>DMSO) 10.05 (1H, bs), 8.62 (1H, s), 8.15 (1H, s), 7.88 (2H, d,  $\downarrow$  7.9Hz), 7.78 (2H, d,  $\downarrow$  8.5Hz), 7.69 (2H, d,  $\downarrow$  8.5Hz), 7.65 (1H, s), 7.55 (2H, d,  $\downarrow$  8.8Hz), 1.42 (6H, s). MS (ESI) 405 (MH<sup>+</sup>, 100%).

1-(4-Aminophenyl)-1H-imidazole used in the above process was prepared by suspending 1-(4-nitrophenyl)-1H-imidazole (10.0g, 52.86mmol) and 10% Pd on carbon (1g) in ethanol (125ml). The mixture was degassed with N<sub>2</sub> and subjected to an atmosphere of hydrogen (balloon) for 24h at room temperature with magnetic stirring. The reaction was filtered through Celite®, washing the filter cake with ethanol (125ml) and the filtrates concentrated *in vacuo* to give 1-(4-aminophenyl)-1H-imidazole as an off white solid (8.02g) m.p. 156-157°.

#### 15 EXAMPLE 4

##### 4-[4-(1-Amino-1-methylethyl)-3-fluorophenyl]-5-chloro-N-[4-(2-hydroxyethyl)phenyl]pyrimidine-2-amine

The title compound was prepared from 4-[4-(1-tert-butoxycarbonylamino-1-methylethyl)-3-fluorophenyl]-2,5-dichloropyrimidine (1.60g, 4.0mmol) and 4-aminophenethyl alcohol (826mg, 6.0mmol) following the method of Example 1.

The crude product was purified by column chromatography (silica; 5-10% MeOH in CH<sub>2</sub>Cl<sub>2</sub>) to give the title compound as a light brown solid (920mg) m.p. 172-176°.  $\delta$ H (CDCl<sub>3</sub>) 8.43 (1H, s), 7.67 (1H, dd,  $\downarrow$  8.2, 1.8Hz), 7.62-7.55 (4H, m), 7.22 (2H, d,  $\downarrow$  8.5Hz), 7.19 (1H, bs), 3.86 (2H, t,  $\downarrow$  6.5Hz), 2.86 (2H, t,  $\downarrow$  6.5Hz), 1.68 (2H, bs), 1.60 (6H, s). MS (ESI) 401 (MH<sup>+</sup>).

The intermediate 4-[4-(1-tert-butoxycarbonylamino-1-methylethyl)-3-fluorophenyl]-2,5-dichloropyrimidine in the above process was prepared using the same methods described for its analogue in Example 1. Thus starting from 4-bromo-2-fluorobenzonitrile the following intermediates were prepared:

*tert*-Butyl N-{1-(4-bromo-2-fluorophenyl)-1-methylethyl}carbamate as an off white solid  $\delta$ H (CDCl<sub>3</sub>) 7.25-7.16 (3H, m), 4.98 (1H, bs), 1.66 (6H, s), 1.36 (9H, bs).

*tert*-Butyl N-{1-[4-(4,4,5,5-tetramethyl-1,3,2-dioxanborolan-2-yl)-2-

fluorophenyl]-1-methylethyl]carbamate as a white solid  $\delta$ H (CDCl<sub>3</sub>) 7.51 (1H, dd,  $\downarrow$  7.7, 1.1Hz), 7.42 (1H, dd,  $\downarrow$  13.0, 1.1Hz), 7.34 (1H, t,  $\downarrow$  8.0Hz), 5.01 (1H, bs), 1.68 (6H, s), 1.33 (21H, bs).

- 5 4-[4-(1-tertButoxycarbonylamino-1-methylethyl)-3-fluorophenyl]-2,5-dichloropyrimidine m.p. 148-149°.  $\delta$ H (CDCl<sub>3</sub>) 8.65 (1H, s), 7.72 (1H, dd,  $\downarrow$  8.3, 1.9Hz), 7.64 (1H, dd,  $\downarrow$  13.1, 1.8Hz), 7.50 (1H, t,  $\downarrow$  8.3Hz), 5.04 (1H, bs), 1.72 (6H, s), 1.37 (9H, s) MS (ESI) 422 (MNa<sup>+</sup>).

### EXAMPLE 5

- 10 4-[4-(1-Allyloxycarbonylamino-1-methylethyl)phenyl]-5-chloro-N-[4-(2-imidazol-1-ylethyl)phenyl]pyrimidine-2-amine

- p-Toluenesulphonyl chloride (867mg, 4.55mmol) was added to a solution of 4-[4-(1-allyloxycarbonylamino-1-methylethyl)phenyl]-5-chloro-N-[4-(2-hydroxyethyl)phenyl]pyrimidine-2-amine (1.16g, 3.03mmol), pyridine  
15 (2.45ml, 30.3mmol) and 4-dimethylaminopyridine (50mg) in CH<sub>2</sub>Cl<sub>2</sub> (25ml). The reaction was stirred at room temperature under N<sub>2</sub> for 18h before diluting with CH<sub>2</sub>Cl<sub>2</sub> (50ml). The dichloromethane solution was washed with 2M hydrochloric acid (2 x 80ml), brine (80ml), dried (MgSO<sub>4</sub>) and concentrated *in vacuo* to give a thick oil. Column chromatography  
20 (silica; 35% ethyl acetate in hexane) gave 4-[4-(1-allyloxycarbonylamino-1-methylethyl)phenyl]-5-chloro-N-[4-(2-ptoluenesulphonyloxyethyl)phenyl]pyrimidine-2-amine as a pale yellow solid (1.40g).  $\delta$ H (CDCl<sub>3</sub>) 8.42 (1H, s), 7.89 (2H, d,  $\downarrow$  8.5Hz), 7.70 (2H, dt,  $\downarrow$  8.4, 1.8Hz), 7.56-7.51 (5H, m), 7.28 (2H, d,  $\downarrow$  8.6Hz), 7.09 (2H, d,  $\downarrow$  8.5Hz), 5.90 (1H, bs), 5.32 (1H, bs),  
25 5.21 (2H, s), 4.51 (2H, d,  $\downarrow$  5.5Hz), 4.20 (2H, t,  $\downarrow$  7.1Hz), 2.93 (2H, t,  $\downarrow$  7.1Hz), 2.41 (3H, s), 1.71 (6H, s).

- To the tosylate prepared above (1.0g, 1.61mmol) in dry DMF (20ml) under N<sub>2</sub> was added imidazole (1.03g, 15.2mmol) and the mixture heated to 80° for 18h. Solvent was removed *in vacuo* and the residue dissolved in  
30 CH<sub>2</sub>Cl<sub>2</sub> (80ml), washed with aqueous Na<sub>2</sub>CO<sub>3</sub> (3 x 20ml), brine (20ml), dried (MgSO<sub>4</sub>) and concentrated *in vacuo*. Column chromatography (silica; 5% methanol in CH<sub>2</sub>Cl<sub>2</sub>) gave 4-[4-(1-allyloxycarbonylamino-1-methylethyl)phenyl]-5-chloro-N-[4-(2-imidazol-1-ylethyl)phenyl]pyrimidine-2-amine as a yellow solid (670mg) m.p. 72-78°.  $\delta$ H (CDCl<sub>3</sub>) 8.41 (1H, s)  
35 7.88 (2H, d,  $\downarrow$  8.6Hz), 7.61-7.52 (4H, m), 7.35 (1H, bs), 7.21 (2H, d,  $\downarrow$

8.5Hz), 5.89 (1H, bs), 5.39-5.13 (3H, m), 4.50 (2H, d,  $\downarrow$  5.6Hz), 3.86 (2H, t,  $\downarrow$  6.5Hz), 2.85 (2H, t,  $\downarrow$  6.5Hz), 1.71 (6H, s). MS (ESI) 517 (MH<sup>+</sup>, 100%).

The intermediate 4-[4-(1-allyloxycarbonylamino-1-methylethyl)phenyl]-5-chloro-N-[4-(2-hydroxy-ethyl)phenyl]pyrimidine-2-amine used in the above

5 process was prepared as follows:

To a solution of the compound of Example 1 (1.20g, 3.1mmol) in CH<sub>2</sub>Cl<sub>2</sub> (40ml) was added saturated, aqueous Na<sub>2</sub>CO<sub>3</sub> (20ml) and allylchloroformate (410mg, 3.4mmol) and the reaction stirred at room temperature for 2h. The CH<sub>2</sub>Cl<sub>2</sub> layer was separated, dried (MgSO<sub>4</sub>) and

10 concentrated *in vacuo*. The crude material was purified by column chromatography (silica; 5% methanol in CH<sub>2</sub>Cl<sub>2</sub>) to give the desired intermediate as a yellow solid (1.23g).  $\delta$ H (CDCl<sub>3</sub>) 8.41 (1H, s), 7.88 (2H, d,  $\downarrow$  8.6Hz), 7.61-7.51 (4H, m), 7.35 (1H, bs), 7.21 (2H, d,  $\downarrow$  8.5Hz), 6.91 (1H, bs) 5.40-5.18 (3H, m), 4.50 (2H, d,  $\downarrow$  5.6Hz), 3.86 (2H, t,  $\downarrow$  6.5Hz),  
15 2.85 (2H, t,  $\downarrow$  6.5Hz), 1.71 (6H, s). MS (ESI) 467 (MH<sup>+</sup>, 100%).

#### **EXAMPLE 6**

##### **4-[4-(1-Allyloxycarbonylamino-1-methylethyl)phenyl]-5-chloro-N-[4-(2-morpholinoethyl)phenyl]pyrimidine-2-amine**

20 A mixture of the tosylate prepared in Example 5 (400mg, 0.64mmol) and morpholine (0.28ml, 3.22mmol) was heated to reflux in dry THF (10ml) under N<sub>2</sub> for 18h. The reaction was diluted with ethyl acetate (40ml), washed with saturated, aqueous Na<sub>2</sub>CO<sub>3</sub> (2 x 20ml), dried (MgSO<sub>4</sub>) and concentrated *in vacuo*. The crude product was purified by column  
25 chromatography (4% methanol in CH<sub>2</sub>Cl<sub>2</sub>) to give the title compound as a yellow solid (310mg) m.p. 65-69°  $\delta$ H (CDCl<sub>3</sub>) 8.41 (1H, s) 7.88 (2H, d,  $\downarrow$  8.5Hz), 7.57-7.52 (4H, m), 7.19 (2H, d,  $\downarrow$  8.4Hz), 7.18 (1H, obscured by over-lapping signal), 5.88 (1H, bs), 5.36-5.19 (3H, m), 4.50 (2H, d,  $\downarrow$  5.6Hz), 3.85 (4H, bs), 3.06-2.43 (8H, m), 1.71 (6H, s).

30

#### **EXAMPLE 7**

##### **4-[4-(1-Allyloxycarbonylamino-1-methylethyl)-3-fluorophenyl]-5-chloro-N-[4-(2-(imidazol-1-yl)ethyl)phenyl]pyrimidine-2-amine**

The title compound was prepared from 4-[4-(1-allyloxycarbonylamino-1-methylethyl)-3-fluorophenyl]-5-chloro-N-[4-(2-p-toluenesulphonyloxyethyl)-phenyl]pyrimidine-2-amine (504mg, 0.79mmol) and imidazole (337mg,  
35



4.95 mmol) following the method described for Example 5. The crude product was purified by column chromatography (silica; 5% methanol in CH<sub>2</sub>Cl<sub>2</sub>) to give the title compound as a yellow solid (330mg) m.p. 88° forms gum.  $\delta$ H (CDCl<sub>3</sub>) 8.43 (1H, s), 7.69 (1H, dd,  $\downarrow$  8.2, 1.8Hz), 7.61 (1H, dd,  $\downarrow$  13.3, 1.8Hz), 7.54 (2H, d, with fine splitting,  $\downarrow$  8.6Hz), 7.50 (1H, t,  $\downarrow$  8.5Hz), 7.34 (1H, s), 7.18 (1H, s), 7.04 (3H, m), 5.89 (1H, bs), 5.30-5.12 (3H, m), 4.50 (2H, dt,  $\downarrow$  5.6, 1.4Hz), 4.16 (2H, t,  $\downarrow$  7.1Hz), 3.03 (2H, t,  $\downarrow$  7.0Hz), 1.78 (6H, s); MS (ESI) 535 (MH<sup>+</sup>, 100%).

The intermediate tosylate used in the above process was prepared using the same methods described for its analogue in Example 5: thus starting from the compound of Example 4 the following intermediates were prepared:

4-[4-(1-Allyloxycarbonylamino-1-methylethyl)-3-fluorophenyl]-5-chloro-*N*-[4-(2-hydroxyethyl)phenyl]pyrimidine-2-amine as a yellow solid.  $\delta$ H (CDCl<sub>3</sub>) 8.42 (1H, s), 7.69 (1H, d,  $\downarrow$  8.2Hz), 7.61 (1H, d,  $\downarrow$  13.4Hz), 7.56 (2H, d,  $\downarrow$  8.4Hz), 7.49 (1H, t,  $\downarrow$  8.4Hz), 7.22 (2H, d,  $\downarrow$  8.5Hz), 7.21 (1H, bs), 5.88 (1H, bs), 5.30 (1H, s), 5.29-5.16 (2H, m), 4.49 (2H, m), 3.86 (2H, t,  $\downarrow$  6.3Hz), 2.86 (2H, t,  $\downarrow$  6.3Hz), 1.78 (6H, s); MS (ESI) 485 (MH<sup>+</sup>, 100%).

4-[4-(1-Allyloxycarbonylamino-1-methylethyl)-3-fluorophenyl]-5-chloro-*N*-[4-(2-*p*-toluenesulphonyloxyethyl)phenyl]pyrimidine-2-amine as a yellow solid.  $\delta$ H (CDCl<sub>3</sub>) 8.43 (1H, s), 7.70 (4H, m), 7.62 (1H, dd,  $\downarrow$  13.3, 1.8Hz), 7.54-7.48 (3H, m), 7.29 (2H, d,  $\downarrow$  8.0Hz), 7.10 (2H, d,  $\downarrow$  8.5Hz), 5.88 (1H, bs), 5.33-5.12 (3H, m), 4.51 (2H, m), 4.20 (2H, t,  $\downarrow$  7.1Hz), 2.94 (2H, t,  $\downarrow$  7.0Hz), 2.42 (3H, s), 1.78 (6H, s).

25

### EXAMPLE 8

#### 4-[4-(1-Amino-1-methylethyl)phenyl]-5-chloro-*N*-[4-(2-imidazol-1-yl)ethyl]phenyl]pyrimidine-2-amine

Tetrakis(triphenylphosphine)palladium(0) (147mg, 0.13mmol) was added to a solution of the compound of Example 5 (655mg, 1.27mmol) and 5,5-dimethyl-1,3-cyclohexanedione (1.42g, 10.15mmol) in anhydrous THF (20ml) under N<sub>2</sub>. The reaction was stirred for 30min at room temperature and was then diluted with ethyl acetate (50ml), washed with 2M aqueous NaOH (3 x 20ml), brine (20ml), dried (MgSO<sub>4</sub>) and concentrated *in vacuo*. The crude product was purified by column chromatography (Silica; 10% methanol in CH<sub>2</sub>Cl<sub>2</sub>) to give the title compound as a yellow solid (380mg).

$\delta$ H (CDCl<sub>3</sub>) m 8.41 (1H, s), 7.86 (2H, d,  $\downarrow$  8.5Hz), 7.64 (2H, d,  $\downarrow$  8.5Hz), 7.55 (2H, d,  $\downarrow$  8.5Hz), 7.36 (1H, bs), 7.34 (1H, bs), 6.99 (3H, m), 6.83 (1H, bs), 4.14 (2H, m), 3.00 (2H, t,  $\downarrow$  7.0Hz), 2.72 (2H, bs), 1.57 (6H, s). MS (ESI) 433 (MH<sup>+</sup>, 100%).

5

The following examples 9 and 10 were prepared by the method described for Example 8.

**EXAMPLE 9****10 4-[4-(1-Amino-1-methylethyl)phenyl]-5-chloro-N-[4-(2-morpholinoethyl)phenyl]pyrimidine-2-amine**

From the compound of Example 6 (310mg, 0.58mmol), tetrakis-(triphenylphosphine)palladium(O) (60mg, 0.06mmol) and 5,5-dimethyl-1,3-cyclohexadione (650mg, 4.64mmol) to give the title compound as a pale yellow solid (240mg) m.p. 166-173°  $\delta$ H (CDCl<sub>3</sub>) 8.40 (1H, s), 7.87 (2H, d,  $\downarrow$  8.4Hz), 7.65 (2H, d,  $\downarrow$  8.3Hz), 7.53 (2H, d,  $\downarrow$  8.3Hz), 7.24 (1H, bs), 7.17 (2H, d,  $\downarrow$  8.4Hz), 3.75 (4H, m), 2.78 (2H, m), 2.58 (8H, m), 1.58 (6H, s). MS (ESI) 452 (MH<sup>+</sup>).

**20 EXAMPLE 10****4-[4-(1-Amino-1-methylethyl)-3-fluorophenyl]-5-chloro-N-[4-(2-imidazol-1-yl)ethyl]phenyl]pyrimidine 2-amine**

From the compound of Example 7 (330mg, 0.62mmol) tetrakis-(triphenylphosphine)palladium(O) (71mg, 0.062mmol) and 5,5-dimethyl-1,3-cyclohexadione (692mg, 4.94mmol) to give after chromatography (Silica; 8% methanol in CH<sub>2</sub>Cl<sub>2</sub>) the title compound as a yellow solid (200mg) m.p. 112-120°  $\delta$ H (d<sup>6</sup> DMSO) 9.85 (1H, s), 8.60 (1H, s), 7.77 (1H, t,  $\downarrow$  8.4Hz), 7.62 (2H, d,  $\downarrow$  8.5Hz), 7.57 (1H, s, with fine splitting), 7.52 (1H, d,  $\downarrow$  1.7Hz), 7.48 (1H, s), 7.12 (1H, s), 7.08 (2H, d,  $\downarrow$  8.5Hz), 6.83 (1H, s), 4.16 (2H, t,  $\downarrow$  7.4Hz), 2.95 (2H, t,  $\downarrow$  7.5Hz), 1.46 (6H, s), MS (ESI) 451 (MH<sup>+</sup>).

**30 EXAMPLE 11****Resin bound 4-[4-(1-tert-butoxycarbonylamino-1-methylethyl)phenyl]-5-chloro-N-[4-(2-hydroxyethyl)phenyl]pyrimidine-2-amine (1)**

35

A slurry of polystyrene sulphonyl chloride resin (Argonaut Technologies, 520mg, 2.4mmol/g, 1.24mmol equivalent) in anhydrous dichloromethane (12ml) was treated with 4-[4-(1-tert-butoxycarbonylamino-1-methylethyl)phenyl]-5-chloro-N-[4-(2-hydroxyethyl)phenyl]pyrimidine-2-amine (2.40g, 4.97mmol), N,N-diethylisopropylamine (0.64g, 4.97mmol) and anhydrous pyridine (4mL) and the resulting mixture agitated at room temperature for 18h. The resin was filtered and washed sequentially with dichloromethane, methanol, N,N-dimethylformamide and dichloromethane then air dried to give the sulphonate derivatised resin (1).

10

**EXAMPLE 12****4-[4-(1-Amino-1-methylethyl)phenyl]-5-chloro-N-[4-(2-(2-methylimidazol-1-yl)ethyl)phenyl]pyrimidine-2-amine**

A mixture of derivatised resin (1) (55mg), N,N-diethylisopropylamine (38mg, 0.30mmol), and 2-methylimidazole (8mg, 0.10mmol) in anhydrous acetonitrile (2ml) was heated at 70° for 18h, with agitation. The mixture was allowed to cool to room temperature then diluted with anhydrous tetrahydrofuran (2ml) and treated with polystyrene methylisocyanate (Argonaut Technologies, 120mg, 1.65mmol/g, 0.2mmol equivalent) and macroporous triethylammonium methylpolystyrene carbonate (Argonaut Technologies, 38mg, 2.64mmol/g, 0.1mmol equivalent). The resulting mixture was agitated at room temperature for 6h, then filtered and washed once with dichloromethane. The combined filtrate and washings were evaporated to dryness under a stream of nitrogen, then resuspended in dichloromethane (1mL) and treated with trifluoroacetic acid (1mL) for 1h at room temperature. The mixture was evaporated to give the title compound (19.4mg).

25

HPLC-MS Retention time 1.93min; MH+ 447

**30 HPLC-MS**

HPLC-MS was performed on a Hewlett Packard 1100/MSD ES Single Quadropole system with diode array detector using a Luna C18(2) 50 x 2.0mm (3µm) column, running a gradient of 95% [0.1% aqueous formic acid], 5% [0.1% formic acid in acetonitrile] to 10% [0.1% aqueous formic acid], 90% [0.1% formic acid in acetonitrile] over 2min, then maintaining the mobile phase at that ratio for a further 1min. Flow rate 0.8ml/min. MS

35

was acquired by API electrospray in positive ion mode, at 70V, scanning from 150 to 750amu.

5 The following compounds of examples 13 to 25 were prepared in a similar manner to the compound of example 12, each using the starting material shown in place of 2-methylimidazole:

**EXAMPLE 13**

10 **4-[4-(1-Amino-1-methylethyl)phenyl]-5-chloro-N-[4-(2-(2-ethylimidazol-1-yl)ethyl)phenyl]pyrimidine-2-amine**  
2-Ethylimidazole gave the title compound (16.1mg)  
HPLC-MS Retention time 1.96min; MH+ 461

**EXAMPLE 14**

15 **4-[4-(1-Amino-1-methylethyl)phenyl]-5-chloro-N-[4-(2-(2-isopropylimidazol-1-yl)ethyl)phenyl]pyrimidine-2-amine**  
2-Isopropylimidazole gave the title compound (12.8mg)  
HPLC-MS Retention time 1.98min; MH+ 475

20 **EXAMPLE 15**

**4-[4-(1-Amino-1-methylethyl)phenyl]-5-chloro-N-[4-(2-(4,5-dichloroimidazol-1-yl)ethyl)phenyl]pyrimidine-2-amine**  
4,5-Dichloroimidazole gave the title compound (20.4mg)  
HPLC-MS Retention time 2.27min; MH+ 501

25

**EXAMPLE 16**

**4-[4-(1-Amino-1-methylethyl)phenyl]-5-chloro-N-[4-(2-(benzimidazol-1-yl)ethyl)phenyl]pyrimidine-2-amine**  
Benzimidazole gave the title compound (16.4mg)  
30 HPLC-MS Retention time 2.04min; MH+ 483

**EXAMPLE 17**

**4-[4-(1-Amino-1-methylethyl)phenyl]-5-chloro-N-[4-(2-(thiomorpholino)ethyl)phenyl]pyrimidine-2-amine**  
35 Thiomorpholine gave the title compound (22.0mg)  
HPLC-MS Retention time 1.93min; MH+ 468

**EXAMPLE 18**

**4-[4-(1-Amino-1-methylethyl)phenyl]-5-chloro-N-[4-(2-(tertbutylamino)ethyl)phenyl]pyrimidine-2-amine**

- 5 tertButylamine gave the title compound (20.4mg)  
HPLC-MS Retention time 1.94min; MH+ 438

**EXAMPLE 19**

**4-[4-(1-Amino-1-methylethyl)phenyl]-5-chloro-N-[4-(2-(4-methylpiperazin-1-yl)ethyl)phenyl]pyrimidine-2-amine**

- 10 1-Methylpiperazine gave the title compound (17.4mg)  
HPLC-MS Retention time 1.84min; MH+ 465

**EXAMPLE 20**

**4-[4-(1-Amino-1-methylethyl)phenyl]-5-chloro-N-[4-(2-(4-ethylpiperazin-1-yl)ethyl)phenyl]pyrimidine-2-amine**

- 15 1-Ethylpiperazine gave the title compound (22.1mg)  
HPLC-MS Retention time 1.85min; MH+ 479

20 **EXAMPLE 21**

**4-[4-(1-Amino-1-methylethyl)phenyl]-5-chloro-N-[4-(2-(3,5-dimethylpiperazin-1-yl)ethyl)phenyl]pyrimidine-2-amine**

2,6-Dimethylpiperazine gave the title compound (3.1mg)  
HPLC-MS Retention time 1.93min; MH+ 479

25

**EXAMPLE 22**

**4-[4-(1-Amino-1-methylethyl)phenyl]-5-chloro-N-[4-(2-(4-(pyrid-2-yl)piperazin-1-yl)ethyl)phenyl]pyrimidine-2-amine**

- 4-(Pyrid-2-yl)piperazine gave the title compound (15.3mg)  
30 HPLC-MS Retention time 1.92min; MH+ 528

**EXAMPLE 23**

**4-[4-(1-Amino-1-methylethyl)phenyl]-5-chloro-N-[4-(2-(pyrrolidin-1-yl)ethyl)phenyl]pyrimidine-2-amine**

- 35 Pyrrolidine gave the title compound (5.6mg)  
HPLC-MS Retention time 1.93min; MH+ 436

**EXAMPLE 24****4-[4-(1-Amino-1-methylethyl)phenyl]-5-chloro-N-[4-(2-(piperidin-1-yl)ethyl)phenyl]pyrimidine-2-amine**

- 5 Piperidine gave the title compound (19.1mg)  
HPLC-MS Retention time 1.94min; MH+ 450

**EXAMPLE 25****(R)-4-[4-(1-Amino-1-methylethyl)phenyl]-5-chloro-N-[4-(2-(3-dimethylaminopyrrolidin-1-yl)ethyl)phenyl]pyrimidine-2-amine**

- 10 (R)-3-Dimethylaminopyrrolidine gave the title compound (23.1mg)  
HPLC-MS Retention time 1.75min; MH+ 479

**EXAMPLE 26**

- 15 **4-[4-(1-Amino-1-methylethyl)phenyl]-5-chloro-N-[4-(2-morpholinoethyl)phenyl]pyrimidine-2-amine maleic acid salt**

- To a hot solution of the compound of Example 9 (50mg, 0.11mmol) in ethanol (2ml) was added a solution of maleic acid (13mg, 0.11mol) in ethanol (1ml) and the mixture stirred at room temperature for 1h. The solution was partially concentrated *in vacuo* and diethyl ether added to give the desired product as a white precipitate. The precipitate was collected by filtration and washed with diethyl ether to give the title compound as a white solid (49mg). m.p. 179-182°.  $\delta$ H (d<sup>6</sup> DMSO) 9.85 (1H, s), 8.64 (1H, s), 8.32 (1H, bs), 7.94 (2H, d, J 8.5Hz), 7.71 (2H, d, J 8.5Hz), 7.64 (2H, d, J 8.5Hz), 7.15 (2H, d, J 8.5Hz), 6.02 (2H, s), 3.61 (4H, bs), 3.31 (3H, bs), 2.69-2.50 (8H, m), 1.69 (6H, s).
- 20  
25

**BIOLOGICAL ACTIVITY**

- 30 The following assays were used to demonstrate the activity and selectivity of compounds according to the invention:

The activity of the compounds against KDR kinase and FGFR2 kinase can be determined in the following two assays:

**KDR Kinase and FGFr2 Kinase**

The activities of recombinant KDR kinase and FGFr2 kinase were determined by measuring their ability to transfer the  $\gamma$ -phosphate from [ $^{33}\text{P}$ ]ATP to polyglutamic acid - tyrosine (pEY).

5

The assay methodology employed for both kinases is identical except that in the assay of KDR kinase the diluent used throughout was 20mM HEPES pH 7.25 containing 2mM  $\text{MnCl}_2$ , 2mM  $\text{MnCl}_2$ , 5mM DTT and 0.05% Brij 35, whereas in the FGFr2 assay 10mM  $\text{MnCl}_2$  is used instead of 2mM  $\text{MnCl}_2$  and 2mM  $\text{MnCl}_2$ .

10

The assay was conducted in a total volume of 202 $\mu\text{l}$  containing 1-10ng kinase, 5 $\mu\text{g/ml}$  pEY (4:1) (Sigma, UK), 1 $\mu\text{M}$  ATP (containing ~50,000cpm [ $^{33}\text{P}$ ]ATP (Amersham International, UK) (Sigma, UK) and test inhibitors at the appropriate concentration. The test inhibitors were dissolved in DMSO and added such that the final concentration of DMSO in the assay did not exceed 2% (v/v). The assay was initiated by addition of kinase and terminated after 10 minutes incubation at room temperature by addition of 50 $\mu\text{l}$  of 20mM HEPES pH 7.25 containing 0.125M EDTA and 10mM ATP.

20 A 200 $\mu\text{l}$  aliquot was applied to the well of a Millipore (UK) MAFC filter plate containing 100 $\mu\text{l}$  of 30% (w/v) trichloroacetic acid (TCA). The plate was then placed on a suitable manifold and connected to a vacuum. After complete elimination of the liquid each well was washed under vacuum using five volumes (100 $\mu\text{l}$  per wash) of 10% (w/v) TCA and finally two

25 volumes (100 $\mu\text{l}$  per wash) of ethanol. The bottom of the filter plate was then sealed and 100 $\mu\text{l}$  per well of Ultima Gold (Beckham, UK) scintillant was added to each well. The radioactivity was measured using an appropriate scintillation counter such as a Wallac Trilux or Packard TopCount. The  $\text{IC}_{50}$  value for each inhibitor was obtained from log dose

30 inhibition curves fitted to the four-parameters logistic equation.

In this assay the most active compounds according to the invention have  $\text{IC}_{50}$  values of around 1 $\mu\text{M}$  and below.

35 The selectivity of compounds according to the invention can be determined in the following assays:

**p56<sup>lck</sup> kinase assay**

The tyrosine kinase activity of p56<sup>lck</sup> was determined using a RR-src peptide (RRLIEDNEYTARG) and [ $\gamma$ -<sup>33</sup>P]ATP as substrates. Quantitation of the <sup>33</sup>P-phosphorylated peptide formed by the action of p56<sup>lck</sup> was achieved using an adaption of the method of Geissler *et al* (J. Biol. Chem. (1990) 265, 22255-22261).

All assays were performed in 20mM HEPES pH 7.5 containing 10mM MgCl<sub>2</sub>, 10mM MnCl<sub>2</sub>, 0.05% Brij, 1 $\mu$ M ATP (0.5 $\mu$ Ci[ $\gamma$ -<sup>33</sup>P]ATP) and 0.8mg/ml RR-src. Inhibitors in dimethylsulphoxide (DMSO) were added such that the final concentration of DMSO did not exceed 1%, and enzyme such that the consumption of ATP was less than 10%. After incubation at 30°C for 15min, the reaction was terminated by the addition of one-third volume of stop reagent (0.25mM EDTA and 33mM ATP in dH<sub>2</sub>O). A 15 $\mu$ l aliquot was removed, spotted onto a P-30 filtermat (Wallac, Milton Keynes, UK), and washed sequentially with 1% acetic acid and de-ionised water to remove ATP. The bound <sup>33</sup>P-RR-src was quantitated by scintillation counting of the filtermat in a Betaplate scintillation counter (Wallac, Milton Keynes, UK) after addition of Meltilex scintillant (Wallac, Milton Keynes, UK).

The dpm obtained, being directly proportional to the amount of <sup>33</sup>P-RR-src produced by p56<sup>lck</sup>, were used to determine the IC<sub>50</sub> for each compound. The IC<sub>50</sub> was defined as the concentration of compound required to reduce the production of <sup>33</sup>P-RR-src by 50%.

In this test, compounds according to the invention have IC<sub>50</sub> values of 10 $\mu$ M and above.

30

**Zap-70 kinase assay**

The tyrosine kinase activity of Zap-70 was determined using a capture assay based on that employed above for p56<sup>lck</sup>. The RR-src peptide was replaced with polyGlu-Tyr (Sigma; Poole, UK) at a final concentration of 17  $\mu$ g/ml. After addition of the stopped reaction to the filtermat, trichloroacetic acid 10% (w/v) was employed as the wash reagent instead of acetic acid

35



and a final wash in absolute ethanol was also performed before scintillation counting. IC<sub>50</sub> values were determined as described above in the p56<sup>lck</sup> assay.

- 5 In this test the compounds of the invention have IC<sub>50</sub> values of around 10 $\mu$ M and above.

#### **EGFr kinase assay**

- 10 The tyrosine kinase activity of the EGF receptor (EGFr) was determined using a similar methodology to the p56<sup>lck</sup> kinase assay, except that the RR-src peptide was replaced by a peptide substrate for EGFr obtained from Amersham International plc (Little Chalfont, UK) and used at the manufacturer's recommended concentration. IC<sub>50</sub> values were determined as described previously in the p56<sup>lck</sup> assay.

15

#### **Protein kinase C assay**

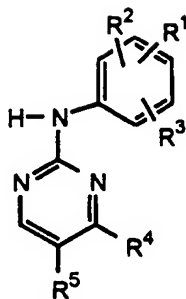
- 20 Inhibitor activity against protein kinase C (PKC) was determined using PKC obtained from Sigma Chemical Company (Poole, UK) and a commercially available assay system (Amersham International plc, Amersham, UK). Briefly, PKC catalyses the transfer of the  $\gamma$ -phosphate (<sup>32</sup>p) of ATP to the threonine group on a peptide specific for PKC. Phosphorylated peptide is bound to phosphocellulose paper and subsequently quantified by scintillation counting. The inhibitor potency is expressed as either (i) the concentration required to inhibit 50% of the enzyme activity (IC<sub>50</sub>) or (ii) the percentage inhibition achieved by 10 $\mu$ M inhibitor.
- 25

In this test the compounds of the invention have IC<sub>50</sub> values of around 10 $\mu$ M and above.

30

**CLAIMS**

1. A compound of formula (1):



5

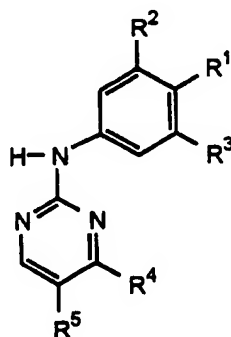
(1)

- wherein R<sup>1</sup> is a -XR<sup>6</sup> group [where X is a covalent bond, -O-, -S-,  
 -C(O)-, -C(S)-, -C(O)O-, -S(O)-, -S(O<sub>2</sub>)-, -CH<sub>2</sub>-, or N(R<sup>7</sup>)- [where R<sup>7</sup>  
 is a hydrogen atom or a straight or branched alkyl group] and R<sup>6</sup> is a  
 10 hydrogen or halogen atom or an optionally substituted aliphatic,  
 cycloaliphatic, heteroaliphatic, heterocycloaliphatic, aromatic or  
 heteroaromatic group, or a -NO<sub>2</sub>, -CN, -SO<sub>2</sub>N(R<sup>8</sup>)(R<sup>9</sup>) [where R<sup>8</sup>  
 and R<sup>9</sup>, which may be the same or different is a hydrogen atom or  
 an optionally substituted aliphatic, cycloaliphatic, heteroaliphatic,  
 15 heterocycloaliphatic, aromatic or heteroaromatic group],  
 -CON(R<sup>8</sup>)(R<sup>9</sup>), -CSN(R<sup>8</sup>)(R<sup>9</sup>), -NH<sub>2</sub> or substituted amino group;  
 R<sup>2</sup> and R<sup>3</sup> which may be the same or different is each a hydrogen or  
 halogen atom or a group selected from an optionally substituted  
 aliphatic, cycloaliphatic, heteroaliphatic, heterocycloaliphatic, -OH,  
 20 -OR<sup>10</sup> [where R<sup>10</sup> is an optionally substituted aliphatic, cycloaliphatic,  
 heteroaliphatic, heterocycloaliphatic, aromatic or heteroaromatic  
 group] -SH, -NO<sub>2</sub>, -CN, -SR<sup>10</sup>, -COR<sup>10</sup>, S(O)R<sup>10</sup>, -SO<sub>2</sub>R<sup>8</sup>,  
 -SO<sub>2</sub>N(R<sup>8</sup>)(R<sup>9</sup>), -CO<sub>2</sub>R<sup>8</sup>, -CON(R<sup>8</sup>)(R<sup>9</sup>), -CSN(R<sup>8</sup>)(R<sup>9</sup>), -NH<sub>2</sub> or  
 substituted amino group;  
 25 R<sup>4</sup> is a X<sup>1</sup>R<sup>11</sup> group where X<sup>1</sup> is a covalent bond or a -C(R<sup>12</sup>)(R<sup>13</sup>)-  
 [where each of R<sup>12</sup> and R<sup>13</sup> is a hydrogen or halogen atom or a  
 hydroxyl, alkyl or haloalkyl group] or -C(O)- group and R<sup>11</sup> is an  
 optionally substituted phenyl, thienyl, thiazolyl or indolyl group;  
 R<sup>5</sup> is a halogen atom or an alkynyl group;

and the salts, solvates, hydrates and N-oxides thereof.

2. A compound according to Claim 1 wherein R<sup>5</sup> is a bromine or chlorine atom.
- 5 3. A compound according to Claim 1 or Claim 2 wherein R<sup>4</sup> is a X<sup>1</sup>R<sup>11</sup> group in which X<sup>1</sup> is a covalent bond.
- 10 4. A compound according to any one of Claim 1 to Claim 3 wherein R<sup>4</sup> is a X<sup>1</sup>R<sup>11</sup> group and R<sup>11</sup> is a phenyl or substituted phenyl group containing one, two, or three R<sup>17</sup> substituents in which each R<sup>17</sup> substituent is an atom or group R<sup>18</sup> or -Alk(R<sup>18</sup>)<sub>m</sub>, where R<sup>18</sup> is a halogen atom, or an amino (-NH<sub>2</sub>), -NHR<sup>19</sup> [where R<sup>19</sup> is an -Alk(R<sup>18</sup>)<sub>m</sub>, heterocycloaliphatic, -Alk-heterocycloaliphatic, aryl or heteroaryl group], -N(R<sup>19</sup>)<sub>2</sub> [where each R<sup>19</sup> group is the same or different], nitro, cyano, hydroxyl (-OH), -OR<sup>19</sup>, formyl, carboxyl (-CO<sub>2</sub>H), esterified carboxyl, thiol (-SH), -SR<sup>19</sup>, -COR<sup>19</sup>, -CSR<sup>19</sup>, -SO<sub>3</sub>H, -SO<sub>2</sub>R<sup>19</sup>, -SO<sub>2</sub>NH<sub>2</sub>, -SO<sub>2</sub>NHR<sup>19</sup>, SO<sub>2</sub>N[R<sup>19</sup>]<sub>2</sub>, -CONH<sub>2</sub>, -CSNH<sub>2</sub>, -CONHR<sup>19</sup>, -CSNHR<sup>19</sup>, -CON[R<sup>19</sup>]<sub>2</sub>, -CSN[R<sup>19</sup>]<sub>2</sub>, -N(R<sup>14</sup>)SO<sub>2</sub>H [where R<sup>14</sup> is a hydrogen atom or a C<sub>1-6</sub>alkyl group], -N(R<sup>14</sup>)SO<sub>2</sub>R<sup>19</sup>, -N[SO<sub>2</sub>R<sup>19</sup>]<sub>2</sub>, -N(R<sup>14</sup>)SO<sub>2</sub>NH<sub>2</sub>, -N(R<sup>14</sup>)SO<sub>2</sub>NHR<sup>19</sup>, -N(R<sup>14</sup>)SO<sub>2</sub>N[R<sup>19</sup>]<sub>2</sub>, -N(R<sup>14</sup>)COR<sup>19</sup>, -N(R<sup>14</sup>)CONH<sub>2</sub>, -N(R<sup>14</sup>)CONHR<sup>19</sup>, -N(R<sup>14</sup>)CON[R<sup>19</sup>]<sub>2</sub>, -N(R<sup>14</sup>)CSR<sup>19</sup>, -N(R<sup>14</sup>)CSNH<sub>2</sub>, -N(R<sup>14</sup>)CSNHR<sup>19</sup>, -N(R<sup>14</sup>)CSN[R<sup>19</sup>]<sub>2</sub>, -N(R<sup>14</sup>)C(O)OR<sup>19</sup>, or an optionally substituted cycloaliphatic, heterocycloaliphatic, aryl or heteroaryl group; Alk is a straight or branched C<sub>1-6</sub> alkylene, C<sub>2-6</sub> alkenylene or C<sub>2-6</sub> alkynylene chain, optionally interrupted by one, two or three -O- or -S- atoms or S(O)-, -S(O)<sub>2</sub>- or -N(R<sup>14</sup>)- groups; and m is zero or an integer 1, 2 or 3.
- 30 5. A compound according to any one of Claim 1 to Claim 4 wherein one or both of R<sup>2</sup> and R<sup>3</sup> is a hydrogen atom.
- 35 6. A compound according to Claim 5 wherein R<sup>2</sup> and R<sup>3</sup> is each a hydrogen atom.

7. A compound according to any one of Claim 1 to Claim 6 wherein  $R^1$  is a group  $-(Alk^2)_pNH_2$  (where  $Alk^2$  is a straight or branched  $C_{1-6}$ alkylene,  $C_{2-6}$ alkenylene or  $C_{2-6}$ alkynylene chain, optionally substituted by one, two or three -O- or -S- atoms or -S(O)-, -S(O)<sub>2</sub>- or -N( $R^{14}$ )- group [where  $R^{14}$  is a hydrogen atom or a  $C_{1-6}$ alkyl group] and p is zero or an integer 1),  $-(Alk^2)_pNR^{15}R^{16}$  [where  $R^{15}$  is an optionally substituted  $C_{1-6}$ alkyl,  $C_{2-6}$ alkenyl or  $C_{2-6}$ alkynyl group optionally interrupted by an -O- or -S- atom or a -C(O)-, -C(S)-, -S(O)-, -S(O)<sub>2</sub>-, -N( $R^{14}$ )-, -CON( $R^{14}$ )-, -OC(O)N( $R^{14}$ )-, -CSN( $R^{14}$ )-, -N( $R^{14}$ )CO-, -N( $R^{14}$ )C(O)O-, -N( $R^{14}$ )CS-, -SON( $R^{14}$ ), -SO<sub>2</sub>N( $R^{14}$ ), -N( $R^{14}$ )SO<sub>2</sub>-, -N( $R^{14}$ )CON( $R^{14}$ )-, -N( $R^{14}$ )CSN( $R^{14}$ )-, -N( $R^{14}$ )SON( $R^{14}$ )- or -N( $R^{14}$ )SO<sub>2</sub>N( $R^{14}$ ) group and  $R^{16}$  is a hydrogen atom or a group as just defined for  $R^{15}$ ],  $-(Alk^2)_pNHet^2$  (where -NHet<sup>2</sup> is an optionally substituted pyrrolidinyl, imidazolidinyl, pyrazolidinyl, piperidinyl, morpholinyl, piperazinyl or thiomorpholinyl group),  $-(Alk^2)_pOH$  or  $-(Alk^2)_pAr$  (where Ar is a nitrogen-containing heteroaromatic group).
8. A compound according to Claim 7 wherein  $R^1$  is a group  $-Alk^2NH_2$ ,  $-Alk^2NR^{15}R^{16}$ ,  $-(Alk^2)_pNHet^2$  (where -NHet<sup>2</sup> is an optionally substituted pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl or thiomorpholinyl group),  $-Alk^2OH$  or  $-Alk^2Ar$  (where Ar is an optionally substituted imidazolyl or benzimidazolyl group).
9. A compound of formula (1a):



(1a)

wherein R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup> and R<sup>5</sup> is each as defined in any one of Claim 1 to Claim 8.

- 5 10. A compound which is:
- 4-[4-(1-Amino-1-methylethyl)phenyl]-5-chloro-N-[4-(2-hydroxyethyl)phenyl]pyrimidine-2-amine;
- 4-[4-(1-Amino-1-methylethyl)phenyl]-5-chloro-N-[3-(2-hydroxyethyl)phenyl]pyrimidine-2-amine;
- 10 4-[4-(1-Amino-1-methylethyl)phenyl]-5-chloro-N-[4-(1-imidazolyl)phenyl]pyrimidine-2-amine;
- 4-[4-(1-Amino-1-methylethyl)-3-fluorophenyl]-5-chloro-N-[4-(2-hydroxyethyl)phenyl]pyrimidine-2-amine;
- 4-[4-(1-Amino-1-methylethyl)phenyl]-5-chloro-N-[4-(2-(imidazol-1-yl)ethyl)phenyl]pyrimidine-2-amine;
- 15 4-[4-(1-Amino-1-methylethyl)phenyl]-5-chloro-N-[4-(2-(2-methylimidazol-1-yl)ethyl)phenyl]pyrimidine-2-amine;
- 4-[4-(1-Amino-1-methylethyl)phenyl]-5-chloro-N-[4-(2-(2-isopropylimidazol-1-yl)ethyl)phenyl]pyrimidine-2-amine;
- 20 4-[4-(1-Amino-1-methylethyl)phenyl]-5-chloro-N-[4-(2-thiomorpholino)ethyl]phenyl]pyrimidine-2-amine;
- 4-[4-(1-Amino-1-methylethyl)phenyl]-5-chloro-N-[4-(2-(tertbutylamino)ethyl)phenyl]pyrimidine-2-amine;
- 4-[4-(1-Amino-1-methylethyl)phenyl]-5-chloro-N-[4-(2-(4-methylpiperazin-1-yl)ethyl)phenyl]pyrimidine-2-amine;
- 25 4-[4-(1-Amino-1-methylethyl)phenyl]-5-chloro-N-[4-(2-(4-ethylpiperazin-1-yl)ethyl)phenyl]pyrimidine-2-amine;
- 4-[4-(1-Amino-1-methylethyl)phenyl]-5-chloro-N-[4-(2-(3,5-dimethylpiperazin-1-yl)ethyl)phenyl]pyrimidine-2-amine;
- 30 4-[4-(1-Amino-1-methylethyl)phenyl]-5-chloro-N-[4-(2-(4-(pyrid-2-yl)piperazin-1-yl)ethyl)phenyl]pyrimidine-2-amine;
- 4-[4-(1-Amino-1-methylethyl)phenyl]-5-chloro-N-[4-(2-(pyrrolidin-1-yl)ethyl)phenyl]pyrimidine-2-amine;
- 4-[4-(1-Amino-1-methylethyl)phenyl]-5-chloro-N-[4-(2-(piperidin-1-yl)ethyl)phenyl]pyrimidine-2-amine;
- 35

and the salts, solvates, hydrates and N-oxides thereof.

11. A pharmaceutical composition comprising a compound according to  
any one of the preceding claims together with one or more  
pharmaceutically acceptable carriers, excipients or diluents.

5

# INTERNATIONAL SEARCH REPORT

International Application No

PCT/GB 00/04043

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D239/42 C07D401/12 A61K31/505 A61P9/14

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

CHEM ABS Data, EPO-Internal

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5 958 935 A (PETER DAVID DAVIS) 28 September 1999 (1999-09-28) column 1 -column 10; claims	1-3, 11
A	WO 99 01439 A (DU PONT) 14 January 1999 (1999-01-14) claims	1-3, 11



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

### \* Special categories of cited documents:

'A' document defining the general state of the art which is not considered to be of particular relevance

'E' earlier document but published on or after the international filing date

'L' document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

'O' document referring to an oral disclosure, use, exhibition or other means

'P' document published prior to the international filing date but later than the priority date claimed

'T' later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

'X' document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

'Y' document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

'&' document member of the same patent family

Date of the actual completion of the international search

14 March 2001

Date of mailing of the international search report

23/03/2001

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2  
NL - 2280 HV Rijswijk  
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,  
Fax (+31-70) 340-3018

Authorized officer

Francois, J

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/GB 00/04043

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
US 5958935	A	28-09-1999	AU 7631496 A	11-06-1997
			EP 0862560 A	09-09-1998
			WO 9719065 A	29-05-1997
WO 9901439	A	14-01-1999	AU 8181098 A	25-01-1999
			EP 0994860 A	26-04-2000
			US 6103737 A	15-08-2000